

CLINICAL CASE OF THE MONTH

A 57-Year-Old Man with an Axillary Mass

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A 57-year-old man presented to the surgical oncology clinic with a mildly tender mass under his right arm. Four years prior, the patient had a melanoma removed from his right shoulder along with an ipsilateral right axillary sentinel lymph sampling. Computed tomography (CT) scan was negative for metastatic disease at that time. The patient did not undergo completion axillary node dissection and was lost to follow-up. The patient was originally from Australia, did not tan but reported multiple sunburns before age 18. He was of Irish ancestry. He denied weight gain, fever, fatigue, anorexia, or night sweats.

The patient had a medical history of atrial fibrillation, hypertension, gout, melanoma, and benign prostatic hypertrophy. His surgical history included an appendectomy and a facial laceration repair. His brother died at 16 years old from leukemia and his mother died from colon cancer. He consumed 3 alcoholic beverages per day and denied tobacco or illicit drug use.

On physical exam, the patient's temperature was 98.8° Fahrenheit, heart rate of 73 beats / minute, blood pressure of 121 / 59 mm Hg, respiratory rate of 18 / min. He appeared to be healthy and in no apparent distress. Cardiovascular, respiratory, breast, gastrointestinal, musculoskeletal, and neurological exam were unremarkable. His right axillary lymph node exam revealed a firm mass roughly 2.5 cm tall by 1.5 cm wide. This mass was biopsied and findings were consistent with metastatic melanoma. CT scan revealed small volume mediastinal adenopathy and a 4.5 cm right axillary mass. There was a 4.7 cm lesion within the anterior left lower lobe of the liver and periportal node conglomerate measuring 3.9 cm consistent with metastatic disease (Figure 1). He was negative for the BRAF V600E mutation.

The patient was consented for treatment with combination immune checkpoint inhibition with ipilimumab and nivolumab. After two cycles the patient showed good response, but temporarily stopped treatment after complications related to a ST segment elevation myocardial infarction. He developed mild pneumonitis felt to be related to nivolumab, and recovered after a short course of glucocorticosteroids. Restaging CT scans were ordered after two cycles of therapy (Figure 2), which showed decrease in the size of the axillary and hepatic metastases. At six months, CT scans showed continued durable response (Figure 3).

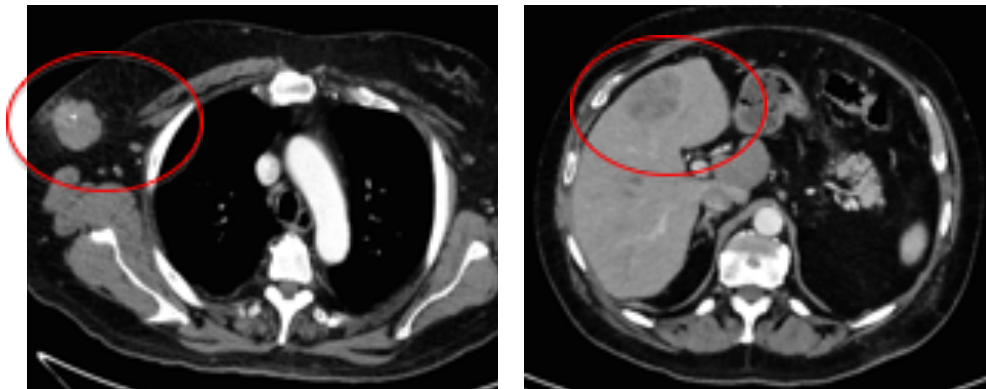


Figure 1. Prior to initiation of Immunotherapy, the patient was found to have a 4.5cm R axillary mass as well as a 4.7 cm liver mass (in red circles)

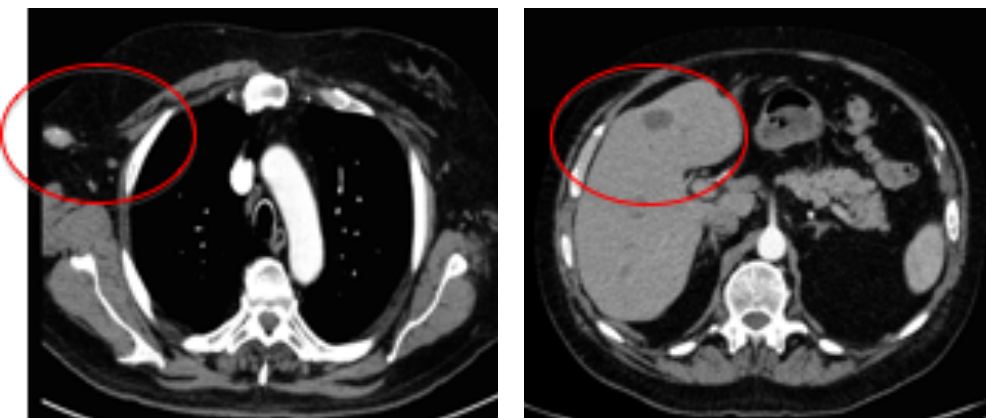


Figure 2. After two cycles of nivolumab and ipilimumab, both the patient's axillary and liver masses decreased in size

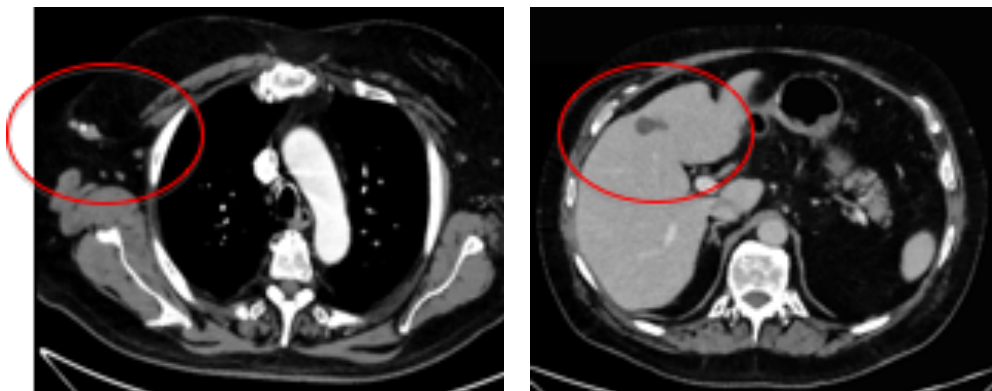


Figure 3. Six months post initiation of therapy, the patient's axillary and liver masses showed continued improvement

EPIDEMIOLOGY

Melanoma is a life threatening form of skin cancer that is most commonly associated with excessive ultraviolet light exposure. It affects roughly one million Americans and is projected to claim over 10,000 lives in 2016.¹ Stage IV, or metastatic melanoma, is thought to be incurable.² Historically, alkylating chemotherapy agents such as dacarbazine and temozolomide have been used with limited efficacy.^{3,4} Interferon- α 2b (IFN- α 2b) and high dose interleukin-2 (IL-2) therapy were mainstays in the treatment of metastatic melanoma; surgical resection is reserved for cases of limited metastatic tumor.⁵

Advances in tumor genomics have recently improved survival rates in patients with metastatic melanoma. For example, a mutation of BRAF is found in half of all melanomas: the V600E BRAF mutation causes unregulated cell proliferation via the MAP kinase pathway.^{6,7} Metastatic melanomas positive for BRAF mutation can be treated with the BRAF inhibitors, vemurafenib or dabrafenib, and can result in a relative reduction of death by 63%.^{3,6} Concurrent inhibition of the BRAF and MEK of the MAP kinase pathway can result in a higher rate of tumor responses and longer duration of responses. Treatment with the MEK inhibitor trametinib combined with dabrafenib has been shown to have an objective response of 76%, with a median progression free survival (PFS) of 9.4 months vs 5.8 months for patients who received dabrafenib monotherapy alone (HR 0.39, $P < 0.001$).⁷

RATIONALE FOR IMMUNOTHERAPY

Recent advances in immunotherapy have provided patients with more durable responses and longer survivals. Metastatic melanomas with and without BRAF mutations may be treated by new immune checkpoint inhibitors, such as nivolumab (anti-PD1 antibody) and ipilimumab (anti-CTLA4 antibody), used in our case patient.

Historically, traditional cytotoxic chemotherapy produced modest benefit. For example, dacarbazine resulted in a low response rate (10-15%) and an overall survival (OS) of eight months.⁸ Interestingly, the immune mediating cytokines also were shown to result in some long-term objective response rates in a limited number of patients. These results suggested that melanoma could be an ideal target for immune manipulation. But, the crude, non-targeted nature of these therapies often resulted in unacceptable toxicities for many patients.

Developments in the understanding of the tumor micro-environment allowed for the ultimate development of more targeted immune mediating drugs. Melanomas are often found to contain tumor-infiltrating lymphocytes (TIL). These cytotoxic T-lymphocytes (CTL) are capable of inducing tumor cell lysis and studies in the 1980s demonstrated the ability of IL-2 to mediate these cells to cause tumor regression in melanomas.^{9,10} Tumors infiltrated with T cells were found to have better long-term patient survival. The mechanism behind a response was thought to be secondary to an active antitumor response by the patient's immune system. This discovery led to therapeutic approaches using recombinant high-dose IL-2 to induce immune-mediated tumor cell lysis in patients with metastatic melanoma.⁹ Several studies demonstrated objective responses in 10-16% of patients treated with high dose IL-2.^{9,10} However, high dose IL-2 treatment is associated with severe toxicity such as vascular leak syndromes, requiring inpatient management. While these factors have limited its generalized use, high dose IL-2 served as proof-of-principle that immunotherapies can be effective.

When grown ex-vivo, TILs exhibit potent antitumor activity. However, in patients, TILs often have a diminished capacity for proliferation, tumor lysis, and cytokine production.¹¹ This implies that the immune climate within the tumor micro-environment (TME) can dampen CTL activity, the result being limited efficacy of IFN- α 2b and IL-2. Understanding of the micro-environment has led to the expansion of today's drug armamentarium.

INHIBITION OF CTLA-4

One mechanism by which T-cells self-regulate is through expression of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a receptor found only on T cells. It functions as a negative co-stimulatory molecule for the T cell.¹² CTLA-4 binds to CD80 and CD86 on antigen-presenting cells and by outcompeting CD28 for binding to CD80 and CD86, CTLA-4 can prevent the co-stimulation needed to maintain T-cell activation (Figure 4).¹³

Ipilimumab is a fully human IgG-1 monoclonal antibody that blocks CTLA-4, resulting in increased T-cell activity and promoting antitumor activity.¹⁴ Two phase-III trials have evaluated ipilimumab in the treatment of metastatic melanoma.^{14,15} In the first trial of patients with treated unresectable stage III or IV melanoma, ipilimumab demonstrated an improved OS versus

glycoprotein-100 peptide vaccine (10.1 vs 6.4 months).¹⁵ The impressive findings from this study were the one and two year OS rates for the ipilimumab arm: 45.6% and 23.5% respectively. Similar rates were seen in the combination arm. The 1-year OS rate was higher than any other experimental regimen for patients with metastatic melanoma. In the second phase III trial, previously untreated patients with metastatic melanoma were treated with ipilimumab plus dacarbazine versus dacarbazine alone.¹⁴ The combination group median OS was superior to the dacarbazine alone group (11.2 vs 9.2 months). In both phase III trials, the response rate was only 10-15% and the disease control rate (complete response, partial response, and stable disease) was 30%. Pooled analysis of 10 prospective and two retrospective studies of ipilimumab as monotherapy in patients with advanced melanoma showed a three year OS of 22%.¹⁶ A substantial number of patients in both trials continued to have long disease control more than five years after completion of therapy.

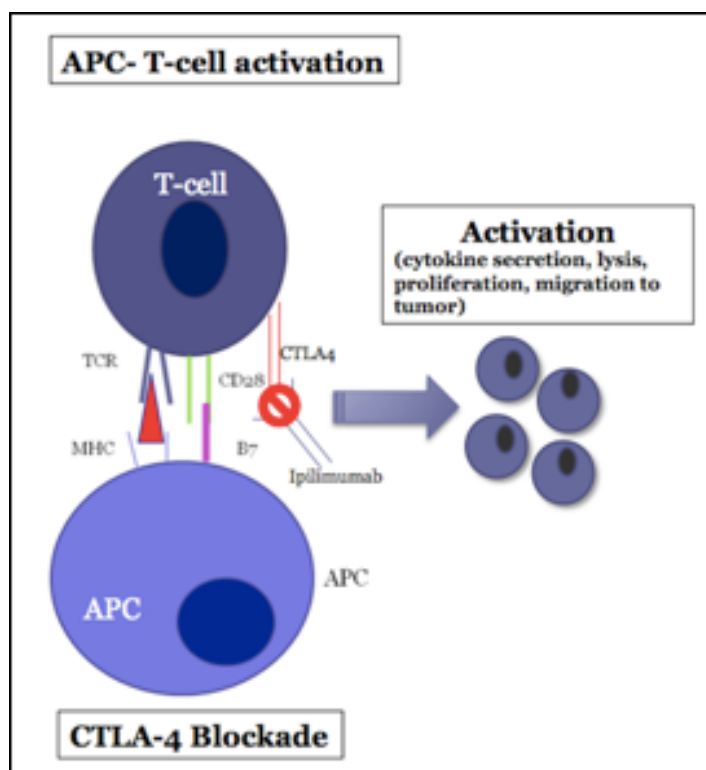


Figure 4. CTLA-4 functions as a negative co-stimulatory molecule on T-Cells. Blocking CTLA-4 maintains T-cell activation and proliferation, which promotes anti-tumor activity.

TCR- T cell receptor, APC- Antigen Presenting Cell, MHC- Major Histocompatibility Complex

INHIBITION OF PD-1

Programmed cell death ligand 1 (PD-L1) is expressed by many cells to induce immune tolerance.¹⁷ The interaction between PD-L1 with the programmed cell death protein 1 (PD-1) receptor on CTLs leads to immune tolerance by causing apoptosis of the T cell.¹⁸ So, for example, melanoma cells expressing PD-L1 on the tumor surface can evade host immune response through this down regulation. Antibodies directed against PD-1 or PD-L1 would be expected to block the down regulatory signal of the tumor and restore antitumor immunity within the tumor microenvironment (Figure 5).

Clinical activity of the anti-PD-1 monoclonal antibody nivolumab has been shown to result in OS rates of 62% at 1 year, 43% at two years, and 41 percent at three years.¹⁹ Data presented at the 2016 American Association for Cancer Research (AACR) Annual Meeting showed a robust five year OS of 34% for patients with advanced melanoma treated with nivolumab.²⁰ The study population had never been treated with ipilimumab and had received between one and five prior therapies for their disease.

Nivolumab has been studied as a second line setting. The Checkmate-037 trial randomized nivolumab versus investigator's choice chemotherapy in patients with advanced melanoma whose disease had progressed after ipilimumab and a BRAF inhibitor administration if the tumor contained a BRAF V600 mutation. The study showed a superior overall response rate (ORR) in the nivolumab group of 31.7%, compared to an ORR of 10.6% in the chemotherapy arm.²¹

Nivolumab has also been studied head-to-head with ipilimumab in patients with metastatic melanoma, in the first-line setting. Checkmate-067 was a randomized phase III trial comparing ipilimumab to nivolumab in patients with advanced melanoma who were naïve to immunotherapy.²² The ORR was 43.7% with nivolumab compared to 19.0% with ipilimumab. Nivolumab also had a longer PFS (HR, 0.57, P<0.001).

A second PD-1 inhibitor, pembrolizumab has shown substantial activity in metastatic melanoma.²³ Pembrolizumab's strong clinical activity was first seen in the phase-1 KEYNOTE-001 trial where pembrolizumab was shown to produce durable responses in both ipilimumab-naïve and previously treated patients with melanoma with an ORR of 33%.²⁴ KEYNOTE-002 was a phase II trial comparing pembrolizumab to physician's choice of chemotherapy in patients with advanced melanoma.²⁵ Superior clinical activity was seen in the pembrolizumab group with an ORR of 25% vs 4% in the chemotherapy arm. Median PFS was 5.6 months vs. 3.6 months in the pembrolizumab and chemotherapy arms, respectively. OS was similar, however, crossover from the chemotherapy to pembrolizumab arms was permitted, making OS assessments difficult.

Like nivolumab, pembrolizumab has also been studied head-to-head with ipilimumab. The Phase III study KEYNOTE-006 compared pembrolizumab versus ipilimumab in patients with melanoma who were naïve to immunotherapy.²⁶ ORR was higher

in the pembrolizumab arm, 33.7% vs. 11.9%. The 6-month PFS rates were 47.3% in the pembrolizumab arm vs 26.5% in the ipilimumab arm.

The data from KEYNOTE-006 and Checkmate-067 confirm the clinical superiority of anti-PD-1 therapy versus anti-CTLA-4 therapy in patients with metastatic melanoma.

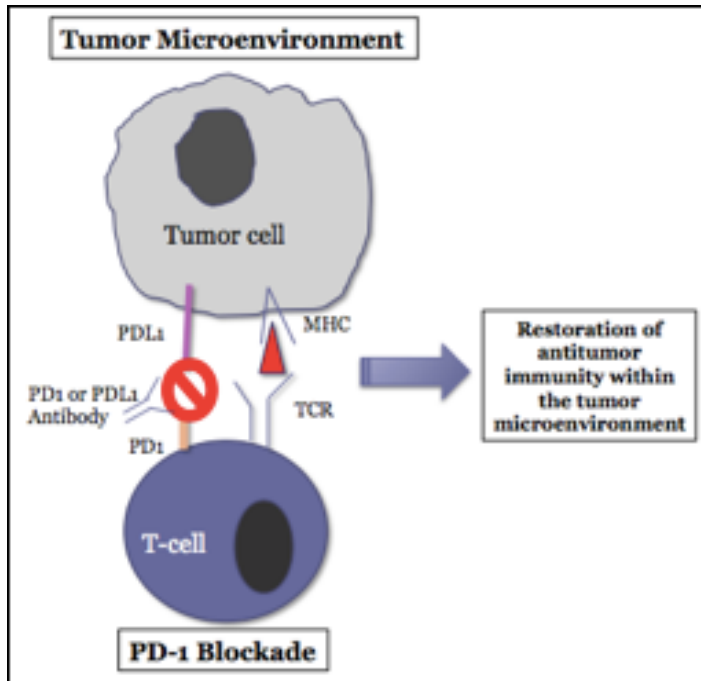


Figure 5. The interaction between PD-1 and PD-L1 can lead to immune tolerance and T-cell apoptosis. By blocking this interaction, antibodies against PD-1/PD-L1 can restore antitumor activity within the tumor microenvironment and activate the immune system to attack tumor cells.

TCR- T cell receptor, MHC- Major Histocompatibility Complex

COMBINATION IMMUNOTHERAPY

Preclinical models have suggested that combining PD-1 and CTLA-4 blockade could alter antitumor activity greater than either strategy alone.²⁷ Combination therapy increased the degree of tumor response and was associated with larger numbers of effector T cells in the TME in murine models. CTLA-4 mediated inhibition of T-cell activation and proliferation occurs at the site of antigen presentation in the lymphoid compartment, while inhibition mediated by the PD-1 pathway occurs at the tumor site. This synergistic concept was studied in several trials, with promising results.

A phase 1 trial of nivolumab and ipilimumab in patients with advanced melanoma demonstrated an ORR of 43% and a two year OS of 79%.²⁸ Subsequently, two randomized trials (Checkmate- 067 and Checkmate- 069) were conducted to further examine combination immunotherapy. Checkmate-069 was a double-blinded phase II trial, randomizing patients to ipilimumab plus nivolumab vs. ipilimumab alone, followed by nivolumab maintenance until disease progression.²⁹ In

patients with BRAF-wildtype tumors, the ORR was 61% in the combination group compared to 11% in the ipilimumab alone group. Median PFS was not reached in the combination group vs 4.4 months in the ipilimumab alone group.

Checkmate-067 was a three arm, double blind, phase III trial that randomized patients to nivolumab alone, nivolumab plus ipilimumab followed by nivolumab maintenance, or ipilimumab alone.²² The median PFS in the combination group was 11.5 months compared to 2.9 months in the ipilimumab group and 6.9 months in the nivolumab alone group. The results from Checkmate-069 and Checkmate-067 studies show that the combination of ipilimumab and nivolumab produces impressive antitumor activity.

IMMUNOTHERAPY TOXICITIES

Despite immunotherapy's benefits, treatment with checkpoint inhibitors is associated with a unique spectrum of side effects termed immune-related adverse events (IrAEs). The most common IrAEs reported have been arthralgia, nausea, diarrhea, fatigue, pruritis, rash, and hypothyroidism. Severe cases of colitis, dermatitis, pneumonitis, and hepatitis have been reported in 1% or less of patients. IrAEs of any grade with ipilimumab occur in the majority of patients, as seen in 64.2% of patients in a pooled analysis of 14 phase I-III studies of ipilimumab.³⁰ Most toxicities are mild to moderate (grade 1-2), involve mainly skin and GI events. Furthermore, the incidence and severity of ipilimumab toxicities appear to be dose related. The rates of severe events (grade 3-5) in anti-PD-1 therapy have been lower than those seen with ipilimumab, occurring in 14% of patients treated with either pembrolizumab or nivolumab.^{23,28} Optimal management of IrAEs includes the early recognition and the appropriately timed use of immunosuppressive agents, such as steroids or anti-TNF- α drugs, based on the severity of the event.

DISCUSSION

The development of checkpoint inhibitor immunotherapy has significantly changed the treatment landscape of advanced melanoma treatment. Anti-CTLA-4 and anti-PD-1 based therapies can produce response rates of above 50% and have been proven to be safer and more effective than traditional therapies such as systemic IL-2. Historically metastatic melanoma has been associated with a poor prognosis, with a median OS of 8-10 months, and a five-year survival of 10%. Immunotherapy has shown to significantly prolong the PFS as well as show a durable response with a 34% five-year response rate for nivolumab monotherapy. Harnessing the body's immune system to target tumor cells is an effective and relatively safe approach to treating such an aggressive disease. As other promising immunotherapies for melanoma proceed through clinical trials, the more we will begin to understand the natural course of melanoma and the interaction between the body's immune system and tumor cells. This understanding will ultimately lead to more treatment options for our patients, and ultimately longer survivals for those affected by advanced melanoma.

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