Evolving Paradigms in Melanoma Therapy

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The Angeles Clinic and Research Institute
Financial Disclosure (Olszanski)

<table>
<thead>
<tr>
<th>Research (FCCC)</th>
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## Financial Disclosure (Hoffner)

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Learning Objectives

1. Discuss basic science behind the human immune response
2. Describe how checkpoint inhibitors, both CTLA-4 and PD-L1, alter the body’s immune response to melanoma cells
3. Describe the mechanism of action for talimogene laherparepvec (T-VEC)
4. Describe potential toxicities associated with checkpoint inhibitors, including etiology of these toxicities and management and/or prophylaxis
5. Explain how checkpoint inhibitors differ from other available treatment options for metastatic melanoma, including kinase inhibitors and cytotoxic chemotherapy
6. Discuss the role of the advanced practitioner as part of the collaborative practice team in caring for patients on immunotherapy treatments
“You should go sit out in the sun. Get some color. You’d look good with a tan. Add a cigarette. I think you’d look really good with a tan and a cigarette.”

Rising Incidence

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2014</th>
<th>Estimated Deaths 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate Cancer</td>
<td>233,000</td>
<td>29,480</td>
</tr>
<tr>
<td>2. Breast Cancer (Female)</td>
<td>232,670</td>
<td>40,000</td>
</tr>
<tr>
<td>3. Lung and Bronchus Cancer</td>
<td>224,210</td>
<td>159,260</td>
</tr>
<tr>
<td>4. Colon and Rectum Cancer</td>
<td>136,830</td>
<td>50,310</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>76,100</td>
<td>9,710</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>74,690</td>
<td>15,580</td>
</tr>
</tbody>
</table>

Survival by Stage

"That’s just great. I discover the cure for the common cold and all you can do is criticize.”
Evolution of Oncologic Care

Oncologic care dominated by trimodality therapy when possible, vs. palliative approaches with each in advanced-disease setting

Immunotherapy is changing the paradigm given the promise of durable disease control in some situations

- Traditional approach → immunotherapy
- Immunotherapy → selective approaches
- Immunotherapy + selective approaches
1953
Mice develop immunity to resected cancer

1957
Interferons discovered

1959
BCG inhibits tumor growth in mice

1973
Dendritic cell discovered
Nobel Prize - Steinman

Adapted from Elert E. Nature. 2013;504:S2-S3.
1975
mAb technology discovered

1983
T-cell antigen receptors discovered

1986
First humanized antibody approved: muromonab

1997
First monoclonal antibody for cancer approved: rituximab

Adapted from Elert E. Nature. 2013;504:S2-S3.
Immunotherapy Timeline (cont)

2008
First cancer vaccine approved worldwide, in Russia, for RCC

2010
Sipuleucel-T approved for prostate cancer

2011
CTLA-4 inhibitor approved for melanoma

2014
PD-1 inhibitors approved for melanoma

Adapted from Elert E. Nature. 2013;504:S2-S3.
Immune System Function

Protects against external threats: viruses, parasites, protozoa, fungi, bacteria, toxins

Immune Response

**Innate**
- Time independent
- Nonspecific
- First line of defense
- WBCs (natural killer cells)
- Recruitment through cytokine upregulation
- Complement cascade
- Activation of adaptive response

**Adaptive**
- Time dependent
- Specific
- Adapts specifically to diverse stimuli
- B-cell antibody production
- T-cell stimulation
- Memory functions
Dual Signals Control Immune Function

The immune system is governed by stimulatory and suppressive interactions

Immune Modulation

- Complex interaction of positive and negative regulatory signals
- Tumor-specific mutations
- Stromal/matrix supportive function
- Immune evasion
- Immune suppression
Immunoeediting Hypothesis

Elimination phase
- Active immune surveillance may eradicate tumor

Equilibrium phase
- Balance between elimination and evasion

Escape phase
- Reduced immunogenicity/enhanced immunosuppression with growth

CTLA-4 and PD-1

Immune Checkpoint Inhibitors
NCCN Guidelines for Metastatic Disease

Systemic Therapy for Metastatic or Unresectable Disease

**BRAF Mutation Status**

- **Metastatic or unresectable disease: BRAF V600 wild type (V600 WT)**
  - Anticipate clinically stable >12 weeks (therapeutic intent: long-term survival)
  - Anticipate clinical deterioration ≤12 weeks
  - Systemic therapy options:
    - Pembrolizumab
    - Nivolumab (category 1)
    - Ipilimumab (category 1)
    - High-dose IL-2
  - Systemic therapy options:
    - Pembrolizumab
    - Nivolumab
    - Ipilimumab (category 1)
    - High-dose IL-2
    - Cytotoxic agents
    - Imatinib for tumors with activating mutations of C-KIT
    - Biochemotherapy (category 2B)

**Disease Status**

- Systemic therapy options:
  - Pembrolizumab
  - Nivolumab (category 1)
  - Ipilimumab (category 1)
  - High-dose IL-2
- Disease progression
- PS 0–2
- PS 3–4

**First-Line Therapy**

- Performance status (PS)
- Systemic therapy options:
  - Pembrolizumab
  - Nivolumab
  - Ipilimumab (category 1)
  - High-dose IL-2
  - Cytotoxic agents
  - Imatinib for tumors with activating mutations of C-KIT
  - Biochemotherapy (category 2B)

**Second-Line or Subsequent Therapy**

Consider best supportive care (See NCCN Guidelines for Palliative Care)

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NCCN Guidelines for Metastatic Disease (cont)

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Anti–CTLA-4 Mechanism of Action

1. Co-stimulation via CD28 ligation activates T cells
   - MHC
   - TCR
   - CD28
   - B7
   - APC
   - Upregulation

2. CTLA-4 ligation down-regulates T-cell responses
   - MHC
   - TCR
   - CD28
   - B7
   - APC
   - Downregulation

3. Blocking CTLA-4 ligation enhances T-cell responses
   - MHC
   - TCR
   - CD28
   - B7
   - APC
   - Ipilimumab
   - Upregulation

Adapted from Fong L, Small EJ. J Clin Oncol. 2008;26:5275-5283.
Survival in First-Line Setting

Ipilimumab Plus Dacarbazine vs. Dacarbazine: OS

<table>
<thead>
<tr>
<th>Patients Surviving (%)</th>
<th>Months</th>
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<tr>
<td>100</td>
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</tr>
<tr>
<td>90</td>
<td>2</td>
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<td>70</td>
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</tr>
<tr>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

- HR (95% CI) 0.72 (0.59–0.87)
- Median OS: 11.2 vs. 9.1 mo
- \( p = .0009 \)

OS = overall survival; HR = hazard ratio; CI = confidence interval.

Survival in Second-Line Setting

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Arms A vs. C</td>
<td>0.68</td>
<td>.0004</td>
</tr>
<tr>
<td>Arms B vs. C</td>
<td>0.66</td>
<td>.0026</td>
</tr>
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</table>

Long-Term Ipilimumab Survival

Immune-Related Adverse Events (irAEs)

- irAEs include any adverse event occurring as a result of the upregulation of the immune system resulting in inflammation and off-target effects of the drug.
- The suffix “-itis” means inflammation, and irEAs can manifest as a variety of “-itis,” which most commonly include:
  - Dermatitis
  - Colitis
  - Hepatitis
  - Hypophysitis
  - Thyroiditis
  - Pruritus
Dermatitis

- Commonly seen with immunotherapy: Up to 40% with anti–CTLA-4 and up to 30% with anti–PD-1
- Can be severe: Stevens-Johnson syndrome, toxic epidermal necrolysis, full-thickness dermal ulceration
  - Median time to onset (anti–CTLA-4): 3 weeks

Images courtesy of Matthew Burke
Dermatitis (cont)

• Mild or moderate dermatitis (rash and pruritus) can be managed symptomatically.
  • Topical nonsteroidal anti-itch cream, antihistamines, oatmeal baths
• If rash persists for more than a week or interferes with activities of daily living, would start moderate-potency steroid creams (triamcinolone 0.1%) OR moderate-dose parenteral steroids at 0.5 mg/kg/day of prednisone or equivalent.
• Serious rashes require discontinuation of ipilimumab and management with high-dose steroids.
• Rapid tapering of steroids is not advised and may result in the recurrence or worsening of symptoms.
• Antibiotics are not helpful.
Diarrhea, abdominal pain, nausea, inability to eat or drink, mucus or blood in the stool

Diarrhea and/or colitis is the most common and potentially most serious complication of anti–CTLA-4 therapy
  - Up to 31% of patients experiencing some grade of diarrhea, with 6% experiencing severe colitis
  - Bowel perforation, sepsis, and death have been reported

Diarrhea and/or colitis is less common with anti–PD-1/PD-L1 therapy
  - Any grade diarrhea ~20%, grade 3/4 diarrhea 1%

Rule out other causes of diarrhea: Clostridium difficile or others

Colitis: Symptoms

- Signs and symptoms to monitor for: Diarrhea, abdominal pain, nausea, inability to eat or drink, mucus or blood in the stool
- Ask patients to report any bowel habit changes promptly and to keep good records of time of day, frequency, volume, and texture
- Rule out other causes of diarrhea, including *C. difficile* or other infectious diarrheas
- **Clinical Pearl:** Colitis can occur without diarrhea; important to take all GI-related symptoms seriously and evaluate
Colitis: Management

- **Mild** (Grade 1): < 4 stools/day above baseline
  - Bland diet, proton pump inhibitors, loperamide ± diphenoxylate/atropine
  - May delay ipilimumab until symptoms improve

- **Moderate** (Grade 2): ≥ 4 to 6 stools/day
  - Consider colonoscopy; moderate-dose steroids: 0.5 mg/kg/day of methylprednisolone; increase dose if no improvement in 24 hours
  - Hold immunotherapy

- **Severe** (Grade ≥ 3): ≥ 7 stools/day
  - High-dose steroids: 1 mg/kg of methylprednisolone or equivalent
  - Discontinue immunotherapy
  - If unresolved within 1 week or symptoms worsen, consider infliximab (anti-TNFα)

- Prevention with budesonide (oral)
  - Randomized phase II trial → no benefit shown

TNFα = tumor necrosis factor alpha.
Hepatitis

- Less common than colitis: < 10% on anti–CLTA-4 and < 1% on anti–PD-1
- Hepatotoxicity appears worse when ipilimumab combined with other drugs, including dacarbazine,¹ vemurafenib,² and anti–PD-1,³ and should be used cautiously
- Symptoms can include
  - Abdominal bloating or pain, dyspepsia, jaundice, and nausea
  - Can be asymptomatic
- Hepatic function (transaminases and total bilirubin) should be monitored at baseline and prior to each dose of treatment
- Abnormal liver function test should be monitored more frequently
- Corticosteroids for grade ≥ 3
- Mycophenolate for persistent severe hepatotoxicity

Hepatitis: Management

- Rule out other causes of liver function test abnormalities
- Increase liver function test monitoring until improvement
- Corticosteroid treatment should be used with grade 3 or higher elevations; prolonged taper may be required
- Mycophenolate may be useful in patients with persistent severe hepatotoxicity
- **Clinical Pearl**: Time-to-onset data not available, but liver function test abnormalities appear to be dose dependent
Endocrinopathies

- Hypothyroidism: Most common endocrinopathy seen with anti–PD-1 (~8%)
- Nonspecific symptoms
  - Headache, fatigue, changes in mental status, abdominal pain, hypotension
- TSH every 12 weeks; follow-up with T3, T4, cortisol, and ACTH and endocrine symptoms do not resolve
- Replacement therapy indicated
- May not be reversible
  - Cosyntropin stimulation test may be helpful prior to starting steroids
  - Can be controlled; if hormone levels stable and ≤ 7.5 mg of prednisone/day, may consider continued immunotherapy

TSH = thyroid-stimulating hormone; ACTH = adrenocorticotropic hormone; T3 = triiodothyronine; T4 = thyroxine.
A variety of autoimmune endocrinopathies have been reported with immunotherapy and can be serious to fatal if not managed correctly.

Hypophysitis first seen with anti–CLTA-4 therapy presented a new form of autoimmune pituitary disease.

Hypophysitis, thyroid disease or abnormal thyroid function tests, and primary adrenal insufficiency have all been reported.

Mechanism of injury not fully understood.

Hypothyroidism is the most common endocrinopathy seen with anti–PD-1 and occurs in approximately 8% of patients.

Endocrinopathies: Symptoms

- Monitor patient for signs and symptoms associated with pituitary, thyroid, or adrenal disease
  - Often nonspecific but may include headache, fatigue, changes in mental status, abdominal pain, hypotension
- Check thyroid function tests at baseline and every 12 weeks while on treatment. TSH is the most sensitive test, but if symptoms, would consider full panel including T3, T4, cortisol, and ACTH
- Time to onset may be much later: Median 11 weeks with anti–CTLA-4 and 14 weeks with anti–PD-1.

TSH = thyroid-stimulating hormone; ACTH = adrenocorticotropic hormone; T3 = triiodothyronine; T4 = thyroxine.

Endocrinopathies: Management

- Treatment of endocrinopathies requires appropriate hormone replacement, corticosteroids, and possibly stopping ipilimumab
  - A cosyntropin stimulation test may be helpful prior to starting steroids.
  - Many endocrinopathies can be controlled and if hormone levels are stable and at less than 7.5 mg of prednisone, then treatment can be continued.

- Clinical Pearl: Does a preexisting thyroid disorder put the patient at higher risk of developing additional endocrinopathies? Not as far as we know.
Kinetics of Adverse Events

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Time (weeks)</th>
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<tbody>
<tr>
<td>Rash, pruritus</td>
<td>0, 2, 4, 6, 8, 10, 12, 14</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>0, 2, 4, 6, 8, 10, 12, 14</td>
</tr>
<tr>
<td>Diarrhea, colitis</td>
<td>0, 2, 4, 6, 8, 10, 12, 14</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0, 2, 4, 6, 8, 10, 12, 14</td>
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Immune Checkpoints

Anti–PD-1

Anti–CTLA-4
Nivolumab vs. Dacarbazine: First Line

Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73)
P<0.001

Patients Surviving (%)

Patients Who Died

<table>
<thead>
<tr>
<th>Patients Who Died</th>
<th>Median Survival</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>no./total no.</td>
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<tr>
<td>Nivolumab</td>
<td>50/210</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>96/208</td>
</tr>
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</table>

Pembrolizumab vs. Ipilimumab

CTLA-4 + PD-1 vs. Single Agent

- Combination is better than any single agent in unselected population
- PD-1 single agent may retain efficacy and decrease AEs in PD-L1–positive patients
- Nivolumab appears better than ipilimumab, even in PD-L1–negative patients

BRAF and MEK

Kinase Inhibition
Vemurafenib vs. Dacarbazine

Overall survival (%)

Hazard ratio 0.70
(95% CI, 0.57–0.87)

\( p < .001 \) (post-hoc)

Vemurafenib (n = 337)
Median f/u 12.5 mo

Dacarbazine (n = 338)
Median f/u 9.5 mo

<table>
<thead>
<tr>
<th>Months</th>
<th>Vemurafenib</th>
<th>Dacarbazine</th>
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<td>178</td>
</tr>
<tr>
<td>24</td>
<td>7</td>
<td>4</td>
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Vemurafenib vs. Dacarbazine: Best Response

SLD = sum of the longest diameter (target lesions).


Vemurafenib: 48.4% response

Dacarbazine: 5.5% response
Dabrafenib vs. Dacarbazaine

Hazard ratio 0.35 (95% CI, 0.20–0.61) (Dec 19, 2011 cut-off)

Proportion Alive Without Progression

Dabrafenib

Dacarbazaine

No. at risk

187 182 167 112 98 39 28 7 4 0

63 53 32 16 12 5 4 2 0 0

Hauschild A, et al. J Clin Oncol. 2012;30 (suppl; LBA8500);
BRAF + MEK: Overall Survival

Overall response rate: 64% vs. 51%
Duration of response: 13.8 vs. 7.5 months

BID = twice daily; DoR = duration of response; ORR = overall response rate; QD = once daily.

Immune + Targeted Therapy?

**BRAF Mutations**

- BRAF mutations found in approximately 50% of melanomas
- Portends more aggressive disease
- BRAF inhibitor therapy associated with 50% response rate and rapid response times
- Acquired resistance to BRAF therapy generally occurs at approximately 6 months
- BRAF and MEK inhibitors are effective only in patients with BRAF V600 mutations

BRAF Inhibition: Adverse Events

Two FDA-approved BRAF inhibitors:
- Vemurafenib
- Dabrafenib

Adverse Events

- **Dermatologic**
  - Potential for severe photosensitivity
  - Squamous cell carcinomas, keratoacanthomas
  - Rash

- **Ocular**
  - Uveitis

- **Cardiac**
  - QTc prolongation

- **Hepatic**

- **General**
  - Alopecia, arthritis, nausea, fatigue

Image courtesy of Brianna Hoffner at The Angeles Clinic
BRAF Inhibitors: AE Management

- **Dermatologic**
  - Skin exam at baseline and every 2 months while on therapy
    - Cutaneous squamous cell carcinoma is the most common grade 3 reaction but does not require a dose reduction
  - No sun exposure; use protection (avoidance, sunscreen, clothing)

- **Ocular**
  - Visual symptoms at each clinic visit
  - Steroid eye drops for uveitis (ophthalmology evaluation)

- **Cardiac**
  - ECG at baseline, day 15, and monthly for 3 months, then every 3 months
  - Hold for QTc > 500 ms or ≥ 60 ms above baseline (grade 3)
  - Restart at a reduced dose if QTc decreases to grade 2

- **Hepatic**
  - Monthly liver function tests (LFTs)
  - Hold for grade 3 LFT and reduce dose when grade ≤ 2

- **General**
  - Nausea → antiemetics
  - Arthralgia → NSAIDs or narcotics
MEK Inhibitors

- Lower single-agent overall response rate ~25% (therefore, use in combination)
- Side effects similar to those with BRAF inhibitors, but also include:
  - Ocular
    - Uveitis
    - Retinal-vein occlusion (discontinue therapy!)
    - Retinal pigment epithelial detachments
  - Cardiac
    - Cardiomyopathy
  - General
    - Peripheral edema (lymphedema, hypoalbuminemia)

MEK Inhibitors: AE Management

- Ocular
  - Permanently discontinue therapy for patients with retinal vein occlusion
  - Perform ophthalmologic exams any time a patient reports visual disturbances; reduce dose for toxicities that resolve or improve

- Dermatologic
  - Dermatologic exam prior to starting therapy and every 2 months until 6 months after discontinuation of therapy
  - For grade 3 or 4 skin toxicity, hold drug for up to 3 weeks. Reduce dose if symptoms improve

- Hepatic
  - Monitor liver function tests at baseline and at least monthly while on therapy. Reduce dose for toxicity

- Hematologic
  - Monitor complete blood cell count. Discontinue for any hemorrhagic event

- Cardiac
  - Assess LVEF prior to initiation of therapy, 1 month after starting therapy and then at 2- to 3-month intervals during therapy
  - Withhold treatment for up to 4 weeks if absolute LVEF value decreases by 10% from pretreatment values and is less than the lower limit of normal

- General
  - Diarrhea can be managed with antidiarrheal medications
  - Therapy should always be held for any intolerable grade 2 or grade 3/4 side effect. Discontinue therapy for second occurrence of grade 4 side effect

LVEF = left ventricular ejection fraction.
BRAF + MEK: Summary

- Combination therapy with dabrafenib and trametinib approved in January 2014
- Response rates from phase I/II trial\(^1\)
  - Overall response rate 76% for combination therapy vs. 54% for single-agent dabrafenib
  - Median duration of response was 10.5 months in combination vs. 5.6% months in dabrafenib monotherapy
- Side effects reported in phase I/II study:
  - Fever (71%)
  - Chills (58%)
  - Fatigue (53%)
  - Rash (45%)
  - Nausea (44%)
  - Vomiting (40%)
  - Diarrhea (36%)
  - Abdominal pain (33%)
  - Peripheral edema (31%)
  - Cough (29%)
  - Headache (29%)
  - Arthralgia (27%)
  - Night sweats (24%)
  - Decreased appetite (22%)
  - Constipation (22%)
  - Myalgia (22%)

- Management and surveillance of side effects based on causative agent and generally as described for single-agent therapies

Case Study 1: History and Physical

- 57-year-old white male
- History of T3b, N0, M0 stage IIB melanoma, s/p WLE 5 yr
- Presents with mild weight loss and fatigue with RUQ pain
- PET/CT imaging demonstrates numerous liver, lung, and abdominal metastasis
- Biopsy of the liver demonstrates melanoma similar to prior

- Medical history: HTN, obesity
- Surgical history: Appendectomy
- Family history: Mother diagnosed with stage II breast cancer, 78 years old, alive and well; father with history of basal and squamous cell skin cancers
- Allergies: No known drug allergies

s/p = status post; WLE = wide local excision; RUQ = right upper quadrant; PET/CT = positron emission/computed tomography; HTN = hypertension.
Further workup/treatment should NOT include which of the following?

A. Brain MRI   JL272
B. *BRAF*-mutation status   JL273
C. Surgical referral for resection   JL274
D. Pain medication   JL275
E. Immunotherapy   JL276
Case Study 1: Treatment Plan

- Patient chose to enroll in clinical trial CA209-218, an expanded-access protocol, to receive ipilimumab 3 mg/kg and nivolumab (anti–PD-1) at 1 mg/kg
- Received cycle 1 on 8/13/2014
- On 8/20/2014, he called the office and noted a mild rash on his back, chest, and legs. The rash was erythematous and intermittently pruritic.
  - Supportive treatment with moisturizing creams and oatmeal bath recommended
- On that same day, he noted that pain in his abdomen and nausea had improved.
Case Study 1: Panuveitis

- On 8/26/2014, patient noted changes in his vision that he described as a “sea of floaters.”
- He was seen by ophthalmology and diagnosed with panuveitis. He was started on prednisone 60 mg po qd.
- He was seen in the clinic on 9/6/2014, and his vision had improved. A 3-week steroid taper was started.
- At that visit, his LDH was 206 IU/L, which was down from a peak of 586 IU/L.

LDH = lactate dehydrogenase.
Case Study 1: Pneumonitis

- On 11/25/2014, restaging CT of the chest, abdomen, and pelvis showed interval improvement of metastatic disease but increased bilateral ground-glass opacities in the lungs. Patient was feeling well and denied any respiratory symptoms.

- On 12/2/14, he developed a dry cough when taking deep breaths. He called the clinic to report these symptoms and was asked to come in for evaluation.

- On presentation to the clinic, his resting oxygen saturation was 96%, but he desaturated to 78% with exertion.

- Chest x-ray showed increased interstitial markings on the periphery of the lungs.
Case Study 1: Pneumonitis (cont)

Chest x-rays showing increased interstitial markings compared to baseline.

Images from the archive of Anthony Olszanski, MD.
Case Study 1: Pneumonitis (cont)

- Patient was admitted to the hospital and started on methylprednisolone at 2 mg/kg.
- A bronchoscopy was performed to rule out causes of infection and to attempt to biopsy the lungs.
  - Cytology was negative.
  - Biopsy of lung parenchyma was consistent with mild chronic inflammation, suggestive of treatment-related pneumonitis.
- Oxygen saturation improved, and the patient was discharged home after 2 days in the hospital on a 4-week steroid taper.
- A follow-up chest x-ray showed less confluent airspace disease in the right lower lobe, but persistent prominence of the interstitium in both lower lung zones and in the periphery. Steroid taper continued.
- Steroid tapered over 1 month. Symptoms of shortness of breath improved. Patient reporting overall improved energy and stamina.
- Restaging scans showed extensive regression of disease.
Case Study 1: Response

Images courtesy of Matthew Burke.
Case Study 2: History and Physical

- 65-year-old white female
- History of T4b, N1a, M0 stage IIIB melanoma, status post wide local excision 3 yr
- Presents with innumerable RLE melanoma lesions
- PET/CT imaging demonstrates no systemic disease
- BRAF testing: V600-mutation–positive

- Medical history: Hypertension, depression, fibroids
- Surgical history: lobular carcinoma in situ removal 2006
- Allergies: Sulfa

Image courtesy of Brianna Hoffner at The Angeles Clinic.
Audience Response Question

What is the LEAST appropriate therapy?

A. Initiate BRAF + MEK inhibition  JL277
B. Start ipilimumab  JL278
C. Perform isolated limb perfusion  JL279
D. Begin nivolumab  JL280
E. Resect visible lesions  JL281
F. Consider an oncolytic clinical trial  JL282
Patient elected to enroll in Amgen 678, a phase Ib/II trial investigating talimogene laherparepvec (T-VEC) in combination with ipilimumab.

- T-VEC is a recombinant oncolytic virus created by modification of herpes simplex virus type-1.
- The gene encoding human granulocyte macrophage colony-stimulating factor (GM-CSF) was inserted to enhance the antitumor immune response through the recruitment of natural killer cells and antigen-presenting cells.
- T-VEC is injected intralesionally and may have a systemic antitumor effect on noninjected tumors.
Case Study 2: Treatment Plan (cont)

- Per protocol, the patient received T-VEC injections only at weeks 1 and 4.
- At week 6, the patient received both T-VEC and ipilimumab.
- Week 8 consisted of T-VEC injections only.
- Week 9 consisted of ipilimumab injections only.

Image courtesy of Brianna Hoffner at The Angeles Clinic.
Case Study 2: Hepatitis

- The patient received the week 9 dose of ipilimumab on 2/24/15. On 3/3/15, she was found to have autoimmune hepatitis, with an ALT of 761 IU/L, AST of 513 IU/L, and LDH of 633 IU/L (all previously WNL).
- She was given a one-time dose of methylprednisolone sodium succinate (125 mg IV) and then initiated on prednisone (80 mg po); labs were checked biweekly.
- A prednisone taper was initiated once liver function tests were WNL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; WNL = within normal limits; ULN = upper limit of normal.
Case Study 2: Response

- Due to a liver function test > 8x the upper limit of normal, the patient’s ipilimumab was discontinued after 2 doses.
- She received T-VEC injections at week 8. Thereafter, she had a CR.

CR = complete response.
Image courtesy of Brianna Hoffner at The Angeles Clinic.
Since 2011, a number of therapeutic options that improve overall survival for patients have been approved.

- **Immunotherapy**
  - Anti–CTLA-4: Ipilimumab
  - Anti–PD-1: Pembrolizumab and nivolumab

- **Kinase inhibitors**
  - BRAF: Vemurafenib and dabrafenib
  - MEK: Trametinib

Some patients experience durable responses.

- Unique adverse events demand attention and communication.
- Exciting new therapies are being developed.
- The oncology advanced practitioner plays an important role in the management of patients with this complex disease.
Evolving Paradigms in Melanoma Therapy

DR. ANTHONY OLSZANSKI: All right. So let’s get to talking about melanoma. We’ll talk about metastatic melanoma. There are some disclosures here. You’ve already had an opportunity to look at the learning objectives so let’s go ahead and start talking about some of the risk factors. Many of you know that the major risk factor for melanoma is in fact UV radiation. This wife is telling her husband, her loving husband, you should sit out in the sun and get some color. You look good with a tan and have a cigarette. I think you’d look really good with a tan and a cigarette. This is sort of exemplifying the risk factors that we probably don’t want to be doing. So melanoma is of course a disease with a rising incidence. It’s one of the cancers with the highest rising incidence today. That’s probably because there is so much UV exposure. It doesn’t matter how we get that UV exposure. It might be sunshine or it might be tanning booths. Over 90% of the U.S. population, and in fact the world population, actually likes to live near the coast. Our bathing suits are getting smaller and we are getting more UV radiation. Melanoma is a very common type of cancer. Actually it’s number five, and I think a lot of people find that somewhat surprising. And you can see that this is really a disease of Caucasians, with whites being misrepresented with the number of patients that are being diagnosed with cancer. This is a survival curve, and you can see the patients with stage 1 melanoma do vastly better than patients, for example, with stage 4 melanoma.
I want to point out one of the problems with this particular curve, and that is in the patients with 2C disease compared to 3A disease, you can actually see that these patients seem to do a little bit worse. 2C disease is usually a disease that has no known involvement, but has ulceration and oftentimes is a relatively deep melanoma, a large mitotic index. 3A is one or two lymph nodes available in a sentinel lymph node biopsy, and so you can actually see there’s some discordance in here in the staging system. It’s important to recognize that your patients with stage 2C disease actually have a fairly high risk. We are going to talk a little bit first, before we even talk about melanoma, about a pivotal need for an understanding of the immune response. In this particular cartoon it says, “That’s just great, I discovered the one cure for the common cold and all you can do is criticize.” We’re going to talk about some of the newer modalities for melanoma, and I think we’ve made leaps and bounds, but they are subject to some of their own side effects. So there’s been a significant evolution of oncologic care. When I started out in my oncology career, we really only had the triumvirate of radiation therapy, surgery, and chemotherapy for every patient. But obviously today, and you certainly hear a lot about that today in and of itself, immunotherapy has really come full circle and is now an integral part of cancer care. It might be given in a traditional approach where you’ll give chemotherapy or radiation therapy all by immunotherapy or sometimes added together. So there’s a lot of new therapies and really new paradigms that we are starting to think about in the treatment of our diseases.
We are going to talk a little bit about the immunotherapy timeline, and I'm not going to go through the whole timeline. Immunotherapy actually began well before we were ever born back in the 1800s, but if we go back to even recent times in 1953, we found that mice developed immunity to resected cancer. In 1957, interferons, which are sometimes used to treat stage 3 melanoma, were discovered. And in 1959, we actually had first evidence of immunotherapy being effective when BCG was found to inhibit tumor growth in mice. And we, of course, use that therapy now for bladder cancer. In 1973 dendritic cells were discovered. 1973 wasn’t too long ago, and we are discovering some special T cells called dendritic cells. In 1975, monoclonal antibody technology was discovered, and we use monoclonal antibodies now every day, but it was actually discovered quite a few years ago. In 1983, the T-cell antigen receptor was discovered. In 1986, we got muromonab, the first humanized antibody approved, and then in 1997, was really the first approval of a major monoclonal antibody, which you all know as rituximab. This timeline continues, and in 2008, the first cancer vaccine worldwide was approved in Russia for renal cell carcinoma. That is now under FDA review for the United States, and in 2010, sipuleucel-T was approved for prostate cancer. In 2011, everything that we once knew about melanoma changed with the approval of the first CTLA-4 inhibitor. In 2011, the first drug that ever showed an overall survival advantage in melanoma was approved.

2011 turned out to be a big year, but it was only the start of many, many big years to come. PD1 inhibitors were approved shortly thereafter in 2014. So
only a year ago we got some other significant advances when it comes to how we treat melanoma based on the immune system. If I take you back to some of your schooling, you'll remember the immune system function is really usually separated into an innate immunity and an adaptive immunity. And those two systems work a little bit independently, as well as codependently. They tend to protect against external threats like viruses or bacteria. The innate immunity is mostly what we think of, is our white blood cell response. The adaptive immunity on the other hand is white blood cells that are specialized like B cells, which produce antibodies and T cells that can produce natural killer cells. The immune responses, innate versus adaptive, are different. The innate is time independent. As soon as you get an infection your innate immunity system kicks in. It's non-specific, it goes after pretty much everything. It's the first line of defense that we have, and it primarily uses white blood cells to identify and phagocytize bacteria, for example.

Whereas the adaptive immune system is time dependent and extremely specific. If you have a bacterial infection, antibodies that are produced only for that bacterial infection. It is very, very specific, and it adapts to very, very diverse stimuli. It is also important to recognize that when we are talking about the immune system, it’s extremely complicated and complex. Brianna and I today are going to be talking about specific tools that we use in the treatment of metastatic melanoma, but I want you to recognize that there are many, many receptor interactions between antigen presenting cells and T cells and between T cells and even the tumor cells. So we might be talking about the interaction of one of
those receptors, but we have to realize that there’s the big milieu of positive and negative regulatory signals. I tried to depict that here in this particular cartoon of immunomodulation. On the top we have certain receptors and they are paired with the receptors on the bottom here.

You can see that this is actually a complex interplay or interaction of both positive and negative regulatory signals. So while we might be treating one signal, we don’t always get the response we are expecting because there are so many other complex signals going on. There are tumor specific mutations and there are also things that we don’t often think about or comprehend, which are the tumor and stromal interactions. There is also the problem of immune invasion and immune suppression. We are going to talk a little about that in a concept that I really want you to try to understand, which is called the immunoeediting hypothesis. We recognize from many, many studies that if in the human life experience in the human lifetime there are probably many neoplastic diseases, which can become problematic for us. In the majority of that time, our immune systems recognize the problem and they get rid of it, and that’s called the elimination phase. We also recognize that some people have cancer, which appears to be stable for very, very long periods of time. That appears to be a balance between both elimination and active evasion. That’s called the equilibrium phase, and patients can exist in that stage for years if not decades. And then there’s also a syndrome, which we know as cancer, called the escape phase, where there’s reduced immunogenicity and enhanced immunosuppression leading to, unfortunately, tumor growth. So now I want to
focus a little bit on some of the immune checkpoint inhibitors and some of the really novel new advances that have occurred again all since 2011. The NCCN Guidelines are a pivotal understanding for the treatment of metastatic melanoma. The NCCN Guidelines were actually just recently updated within the last week or two.

I am part of the NCCN Guideline panel, and I asked to have these slides included, but these are actually old, right? I had this slide done in August and now we have a new update, so the next two slides, which were usually for BRAF negative patients and BRAF positive patients, have now been combined into one slide. But the idea still exists that if you go to the NCCN guidelines, you'll understand that there are certain first-line therapies that we recommend or recognize and second-line therapies as well. I think they are important guidelines to take a look at when you are treating your patients with metastatic melanoma. I am just going to advance through those two slides to get to this cartoon, which is a cartoon we'll see again, but I want you to focus on the bottom part of this cartoon, which is looking at interactions again between a T cell and an antigen-producing cell.

I already told you that this interaction is very complex in a lot of different receptors, but we are going to focus really on the receptor called CTLA-4, which is being produced by T cells and B7, which is produced by the antigen presenting cells. When this receptor engages, it actually turns off the T cell response. So the antigen-presenting cell normally presents an antigen and that antigen is presented to the T cell, and the T cell gets excited and tries to go attack
wherever that antigen is. If we didn’t have a mechanism to turn that function off, we think that we would have a lot of autoimmune problems. Fortunately, we don’t see as many autoimmune diseases as we probably would if we didn’t have some mechanisms to suppress our immune function. So the CTLA-4 receptor produced by T cells actually suppresses that, but we now have a drug call ipilimumab. It’s an anti-CTLA-4 inhibitor and basically it blocks that interaction to keep T cells engaged and stimulated. So if we look at the mechanism of action of this immune checkpoint inhibitor, we have in cartoon box number one as costimulation. This is a costimulation between the antigen presenting cell presenting the antigen to the T cell receptor, the T cell then gets engaged and stimulated and tries to attack whatever is carrying that antigen. But as I mentioned, CTLA-4 then comes up on the T cell. It’s expressed and it binds to B7 just like CD28 does, but that binding is actually much stronger and tighter, preferentially so, and it shuts down the T cell response. Obviously we want that to prevent autoimmune disease, but we don’t want that if we are trying to get an antitumor response. SO CTLA-4 inhibitors like ipilimumab block that interaction and they keep CD28 and B7 engaged, allowing the T cell to stay stimulated. So ipilimumab has been tested in a number of different populations.

The first population we’ll talk about in the first-line setting here where ipilimumab plus chemotherapy. What we commonly used back then, that we don’t commonly use it anymore, was dacarbazine. So this was an ipilimumab plus dacarbazine trial versus dacarbazine itself, and this is an overall survival curve. You’ll see that this overall survival curve has a hazard ratio of about 0.7,
suggesting the ipilimumab imparted about a 30% improvement against the risk of death at any point in time. And I want you to focus on really the tail end of this curve here because the tail end of the curve gets really quite flat. We are pretty excited about that tail end of the curve, and we’re going to talk about that in a minute here. We also saw survival in the second-line setting. In this particular trial, ipilimumab was combined with a vaccine that we thought might have some efficacy called GP100; it was given alone and it was compared to GP100 alone. In this particular slide, both of the ipilimumab arms did significantly better than did the GP100 alone arm again, and this was statistically significant again, demonstrating that we have now established the first drug to improve survival in melanoma. I have talked a little bit about the fact that some of these responses appear to be extremely durable. If you look at this Kaplan-Meier curve of overall survival, you’ll see ipilimumab depicted there by the blue line, and we are looking at survival all the way out to five years. Now mind you, the median survival from melanoma untreated is about six to seven months. With ipilimumab, it did not change the median survival rate very much, but what it did do was increase the population that was having durable disease control. I’m sure Brianna has many patients like this.

I certainly have many patients who have been treated with ipilimumab years ago and are now under surveillance without evidence of disease, and that’s truly remarkable for a disease that would universally kill our patients. Let’s pass through the time a little bit and have Brianna talk a little bit about the immune related events, which we need to know about.
**MS. BRIANNA HOFFNER:** Yes, we are going to talk about the immune related adverse events that we see with these drugs that have given us such great responses, but certainly there are some side effects. So IRE’s include any adverse event that occurs as a result of aggregation of the immune system, which causes inflammation and off target effects from the drug. So we consider IRE’s to be anything that ends in -itis since –itis just means inflammation. We’ve seen all sorts of -itis’ that we never really knew existed since we started using these drugs. The most common things that we see are dermatitis, colitis, hepatitis, hypophysitis, thyroiditis and pruritus, and we are going to talk about these a little bit more in detail.

**DR. ANTHONY OLSZANSKI:** I’m feeling itchy.

**MS. BRIANNA HOFFNER:** Okay, let’s talk about that. So for dermatitis, this is a rash of course. This is something that we came to know really well with the antiCTLA4 drugs because this was a big problem. Up to 40% of patients on antiCTLA4 developed dermatitis, and then on the PD1s it was up to 30%. So the rashes were more severe with the CTLA4s, and for those we could see some of the Stevens-Johnson type syndromes or toxic epidermal necrolysis. And so you can see a picture here of a patient who received ipilimumab and developed a rash. For the PD1s the rashes have not been quite as severe. We do have the median time to onset data for the CTLA4 drugs, since those have been around longer. We know that this tends to be the first IRE to manifest after dosing, and the time is about three weeks. For PD1s, the time to onset is less clear. So for mild to moderate dermatitis, you can manage symptomatically, telling your
patients to take short tepid showers, not long hot showers, and use the unscented creams. They can use antihistamines if they are having any itching associated with it, and then they can use over-the-counter 1% hydrocortisone creams. If that's not working or if the rash is getting worse, you can increase to something with a higher potency like triamcinolone 0.1% cream. If that doesn't work, then you have to go to oral steroids. For something moderate, I would start with 0.5 mg/kg per day of prednisone or the equivalent.

For serious rashes, you have to discontinue drug and manage with high dose steroids. Rapid tapering of steroids is not recommended with these IRAEs because it tends to manifest in recurrence of whatever the issue was. And these rashes tend to be more macular in nature than popular, so we haven't found that antibiotics have been very helpful in the management. So colitis, inflammation of the colon, can manifest as diarrhea, abdominal pain, nausea, inability to eat or drink, or mucus or blood in the stool. Again, this is something that was a big problem with the antiCTLA4s. Up to 31% of patients on CTLA4 had some grade of diarrhea, and we saw 6% with severe colitis. We have seen deaths with the CTLA4s due to bowel perforation, so this is something that we take very, very seriously. Diarrhea or colitis is less common with the PD1s and PDL1s. Any grade diarrhea occurred about 20% of the time, with grade 3 to 4 diarrhea only 1% of cases. It is important to know that you can have colitis without diarrhea. Sometimes the patient who came in, like last week I had a patient who was having her regular bowel movements, but she had a lot of abdominal pain. She was due for scans that day for staging, and her scans showed actually a very
severe pancolitis. So she was started on steroids, but again she did not have any diarrhea at that time, and her symptoms of abdominal pain did resolve with the steroids.

Also, it’s important to keep in mind that you’ve got to rule out other things. If they are having diarrhea, make sure especially if they have been in the hospital recently that they don’t have *Clostridium difficile* or ova and parasites or things like that. So for mild diarrhea you know you need to know your patient’s baseline. Everybody has a different number of bowel movements per day and so if less than four stools is above their baseline you can do dietary changes. The first things you cut out are dairy, so that’s ice cream, which is a problem, alcohol, always a problem to cut out, caffeine, nearly impossible, and spicy foods. The patients are not that compliant with your modifications to their diet. You can also add proton pump inhibitors, which can sometimes help settle down the inflammation. Tell them to take two Imodium after every loose bowel movement. Tell them not to read the box, it doesn’t matter what the box says. Take two Imodium after every loose bowel movement. If that’s not working, you can add Lomotil, which has a little bit of atropine in it. You would delay therapy until the symptoms improved. For moderate colitis, which is more than four to six stools above baseline, you could consider a colonoscopy.

This is a bit controversial because you have a gut that’s already inflamed, and so certainly you wouldn’t want to add any instrumentation that could increase the risk of perforation. If you do a colonoscopy, generally it’s a flex sig; however, you can also diagnose symptomatically or you can use a CT scan as I just
described. You would use moderate dose steroids at 0.5 mg/kg per day of methylprednisolone, and then increase if there’s no improvement within 24 hours. For severe colitis, you’ve got to discontinue the immunotherapy, start high dose steroids 1 mg/kg per day. Keep in mind that this is colitis, so this is really affecting their whole GI tract so they may not absorb an oral steroid. You may have to use IV steroids for these patients, and if it doesn’t resolve or it doesn’t improve, you can consider adding an anti-TNF-alpha drug such as infliximab. A lot of us are familiar with budesonide from bone marrow transplant and the graph versus host disease of the gut where that has been a helpful drug. But we tried that with the colitis related to these drugs in a randomized phase two trial, and there wasn’t any benefit.

So hepatitis is less common than colitis. It’s less than 10% of patients on the antiCTLA4s and less than 1% on the antiPD1s. One thing that we do know about hepatitis, which is incredibly important to keep in mind in the setting of the new approvals that we’ve gotten in the last few weeks, is that when you combine ipilimumab with other drugs such as dacarbazine, vemurafenib, or a PD1, the toxicity is much worse. So given that we just had approval of an antiCTLA4 and antiPD1, please keep in mind that the hepatotoxicity can be severe and life threatening. Symptoms here can include abdominal bloating or pain, dyspepsia, jaundice, and nausea. They can be really vague, and oftentimes they come in with no symptoms. My patient on combination therapy came in last week with an AST of 1,000 and didn’t have a single symptom. Keep in mind that you’ve got to check their liver function tests on these drugs. Abnormal liver function tests
should be monitored more frequently, and then you use corticosteroids for grade 3 or higher and you can add mycophenolate for persistent or severe hepatotoxicity. Endocrinopathies. So hypothyroidism was the most common thing that we saw with the antiPD1 studies. In about 8% of patients. There’s other endocrinopathies of course that we have seen like hyperthyroidism, adrenal insufficiency, and hypophysitis. The symptoms associated with these can be non-specific, you know fatigue, headaches, changes in mental status, hypotension, so you need to be monitoring their thyroid function every 12 weeks and you should replace if they have any insufficiencies there. If they have adrenal insufficiency, you can replace with hydrocortisone. If they are hypothyroid, you can replace with levothyroxine. If they are hyperthyroid, you can manage that either medically with something like methimazole or you can refer them for an ablation procedure.

This is the one immune related adverse event in the endocrinopathy category where we see that it might not be reversible. So the patients who become hypothyroid and require Synthroid, they tend to continue requiring Synthroid. This doesn’t really get it resolved. So it is an important conversation to have with your patients. Management, kind of just talked about that in terms of adding any sort of hormonal replacement that they may require. For a hypophysitis, which is the inflammation of the pituitary, that’s something that you can diagnose symptomatically or you can get an MRI with pituitary cuts for a definitive diagnosis. That can be managed with steroids. Prednisone can get rid of those symptoms, and if you get them down to 7.5 or less you can reinitiate the
immune therapy. One thing that people have asked is whether a preexisting thyroid disorder puts you at higher risk of developing other endocrinopathies. So far, the data has shown that that is not the case. This is a kinetics of adverse events graph, and this is related to antiCTLA4. This is what I was saying. That we don’t have this data yet for the PD1s. As Tony was saying, they were just approved in 2014, and they got accelerated approval. Pembrolizumab was approved off of a phase 1B trial, which is crazy you know, so we are still getting a lot of information about these drugs. But here for the CTLA4s, which have been around longer, you can see that the first toxicity we see is rash, then the diarrhea, then the liver toxicity and the hypophysitis. You can see that the tail there on the hypophysitis kind of keeps going because that one tends not to resolve.

DR. ANTHONY OLSZANSKI: Bri, it sounds to me like early recognition and early management are really the key to the management of the adverse events, and the IPC may be in the best position to do that.

MS. BRIANNA HOFFNER: Absolutely. Yes.

DR. ANTHONY OLSZANSKI: Well, let’s talk a little bit about the PDL1 axis now. We have already seen the slide. I want you to focus on the left-hand side where we are looking at the interaction between the T cell and the tumor cell. And just like CTLA4, the tumor cell produces PDEL1. That can engage with PDE1 on the T cell and put that T cell to sleep. We don’t want that to happen. We give them antiPD1 antibody and it wakes that T cell back up. We find that this particular interaction leads to a more specific immune response. It may be why
we see more side effects with the antiCTLA4 inhibitors because that’s relatively non-specific as opposed to the PDE1 inhibitors, which are relatively specific in engaging with the tumor cell. So nivolumab is a PD1 inhibitor and this first-line study versus dacarbazine. You can see pretty clearly here that looking at survival of patients, nivolumab bested dacarbazine by really quite a bit. Also importantly, you see that dacarbazine line is continuing to fall and, surprisingly, maybe the nivolumab seems to be plateauing out.

This is still a relatively early look at the data, but we are really excited about the durability again of the response of the immunotherapy. The hazard ration for death here is 0.42, that’s suggesting a 60% reduction in the risk of death with a PD1 inhibitor compared to chemotherapy, and that is truly monumental in the treatment of metastatic disease. We also have pembrolizumab, also another PD1 inhibitor. This one is looking at it compared to what also was a good drug; ipilimumab, CTLA4 inhibition in metastatic melanoma, and pembrolizumab in this particular trial was given in two different doses. You can see that both of those doses appear to be doing better than ipilimumab again for a number of patients surviving longer. The time on this graph is only out to 18 months and we still have a lot to learn, but it looks pretty clear that pembrolizumab is again going to do a lot better than just antiCTLA4. But then that begs the question what happens if we actually combine these. Maybe in what is the most important month in melanoma history has just occurred in October of 2015, when three drugs were approved by the FDA in different facets of the treatment of melanoma. We had ipilimumab approved in
the adjuvant setting, we had TVAC approved in the metastatic setting, and we now have both the CTLA4 and the combination with PD1 approved in the metastatic setting. In this particular trial they used ipilimumab plus nivolumab versus single agent nivolumab or ipilimumab. You can see here in the intention to treat population, the combination did better than either agent alone. Again, this particular progression free survival hazard ratio was 0.42. These are amazing hazard ratios again suggesting that we are bettering 60% of the population by decreasing the risk of progression by 60% for death. That’s really amazing. We don’t yet have overall survival data, but I’m an optimist and I think it’s going to be really, really good.

This is the intention to treat population. I would encourage you to go to the article here because it breaks it down into other populations. This is just one example with the PDL1 negative. You can see that in patients that are PDL1 negative, it looks like the combination is again doing better. I want to make a point that we do not need to test PDL1 positivity when selecting out patients for these particular drugs, and I think that’s important. Let’s move away from immunotherapy, which you can obviously see I’m pretty excited about and you can see from Brianna that it has some challenges that we need to recognize. Let’s move instead to the kinase inhibition because this is the second class of drugs that has made a major impact in the treatment of metastatic melanoma. In this particular trial it was vemurafenib and a BRAF inhibitor against a very commonly used back then chemotherapy dacarbazine, and here the hazard ratio was 0.7 for survival. You can see that the BRAF inhibitor clearly did better than
dacarbazine with a median survival of 13½ months for the BRAF inhibitor, versus only about 9.7 months for dacarbazine. So BRAF inhibitors were the second class of drugs to show a survival advantage in melanoma. This is all occurring within the last four years. This is really, really astounding. This is a waterfall plot. The waterfall plot depicts how many patients have some kind of clinical benefit.

Anything underneath the dotted line is some tumor reduction. If you look at the top part of the graph, the top half part of the graph, you can see that patients who were treated with vemurafenib had an astounding 50% response rate. Compare that with the bottom of the graph where patients, who were treated with chemotherapy dacarbazine, had a response rate that we were all too familiar with of only 5%. So a BRAF inhibitor in a patient who is BRAF positive, and only in a patient who is BRAF positive, has a five times better response rate than chemotherapy alone. Dabrafenib is just another example of a BRAF inhibitor, also FDA approved and also showing a survival advantage. This is a graph showing its progression-free survival against dacarbazine. You can see the progression-free survival nearly tripled with the dabrafenib compared to the dacarbazine. And again, just like the checkpoint inhibitors, what happens if we add drugs together? In this example, we’re adding BRAF inhibitors plus MEK inhibitors. I didn’t show you the single agent data on the MEK inhibitors, but suffice it to say that they also may have a role in the treatment of BRAF positive patients. This trial is combining trametinib and dabrafenib. Dabrafenib is the BRAF inhibitor and trametinib is the MEK inhibitor. This trial is showing a survival advantage against the other BRAF inhibitor vemurafenib. So when we have a
patient who is BRAF positive in front of us and we think we want to treat them with a kinase inhibition, we are usually today using the combination.

You can see the response rate is 64% versus 51%. Over half of your patients, regardless of how you treat them, are going to respond and that is pretty astounding. Let’s contrast this with CTLA4 with single agent CTLA4 inhibition with ipilimumab. The response rate is about 10% and for single agent PD1 inhibition, the response rate is somewhere around 40%. If we actually add the CTLA4 and the PD1 inhibitors, we see response rates, which are now approaching 60%. So actually it looks like that combination immunotherapy is getting responses as high as this as well. The response with BRAF and MEK inhibition is where these waterfall plots can be astounding. You can see an overall response rate in this particular earlier clinical trial of 75%. The majority of your patients will do better with these drugs, but we have to be attendant to some of the side effects, which Brianna will talk about. So what happens if we combine therapies from outside of their groups? What if we took a checkpoint inhibitor – I already told you that with the ipilimumab it only has a response rate of about 10%. It has that promise of durable disease control, being alive at five years, and what if we combine that with a BRAF inhibitor, which we have already said has a response rate of 50%. If we combine those, perhaps we can increase the response rate and increase that durability and really get to that C word, not cancer, but cure. Brianna?

**MS. BRIANNA HOFFNER:** Yes. So talking about BRAF mutations, you know because the data is incredibly exciting, the patients do have to have a
BRAF mutation to treat them with these drugs. This is something that we try to drive home, because certainly we have seen in the community, people using these drugs in BRAF wild type patients, and that’s a dangerous thing to do. So BRAF mutations are found in about 50% of melanomas. We do know that BRAF mutated melanomas are a bit more aggressive, but BRAF inhibitors are associated with about a 50% response rate and rapid response times. You literally see tumors melting away from these patients. I had a patient who came in and she could not walk, she was in a wheelchair. She had a big sacral mass, like parasacral, and we started her on a BRAF inhibitor. She walked into the clinic the next day to tell us how much better she was feeling. So they truly can work within 24 hours. We call it the Lazarus effect, but median time to response is about six weeks.

Unfortunately, we do see an acquired resistance with these BRAF therapies. The tumor starts to outsmart it and the acquired resistance comes at approximately six months. BRAF and MEK inhibitors, as we said, are used in patients with the BRAF mutation. It says here, only BRAF V600 mutations, V2 BRAF inhibitors that are approved, are approved for V600. This is a big gene though, so if you send off testing, you may get results that come back with other mutations. So some of the significant adverse events that you can see with BRAF inhibitors, dermatologically, they can be very, very photosensitive. By that I mean that they can go out in the sun for less than five minutes and have grade 3 blistering sunburns that are just horrific. Some people can go out in the sun and have no increased photosensitivity, and we have no way of predicting who’s who.
So you’ve got to do a lot of education before you start your patients on these drugs. Talk to them about avoiding the sun, about using SPF clothing, making sure that everything is covered, always having at least SPF 30 sunscreen on, and to remember the areas that we always forget, which is the tops of our ears, the tops of our feet, the backs of our hands and our lips. Those are the places where we tend to see the worst sunburns, and it’s so sad because then they can’t eat because they have horrible sunburns on their lips.

Also we can see an increase in squamous cell carcinomas with the BRAF inhibitors. They need to be monitored for those and keratotic acanthomas. They can also get new melanomas on the BRAF inhibitors. In terms of ocular toxicities, we see uveitis, which is inflammation of the uvea and manifests as blurred vision or spots in the vision. Cardiac-wise, we see QTC prolongation. We can see hepatic toxicity, and then generally you can see alopecia, arthritis, nausea, and fatigue. So for monitoring and management for the dermatologic issues, we recommend that they get skin exams at baseline and then every two months, while they are on therapy. If they develop a squamous cell carcinoma, it should be excised, but you can continue on the same dose without any dose reduction. For ocular, we recommend asking about any visual symptoms at every visit. If they have any sort of visual complaints, send them to an ophthalmologist to evaluate for uveitis. Generally uveitis can be treated with steroid eye drops, and it resolves fairly quickly. Cardiac-wise, because I said that you can have a prolonged QTC on this drug, they need a baseline ECG and then another one at treatment day 15, at one month, and every three months thereafter. If their QTC
is greater than 500 ms or has increased by more than 60 ms from baseline, you do need to hold the drug until it resolves or decreases, and then you can resume the drug at a decreased dose. For hepatotoxicity, you should monitor their liver function, testing at least monthly. We tend to monitor a bit more closely than that. Hold for grade 3 LFT abnormalities, and then you can dose reduce and resume when it improves.

And then there is the stuff we all know how to manage. Nausea with antiemetics, and the arthralgias associated with BRAF inhibitors are best managed really with NSAIDs rather than narcotics. It tends to be more inflammatory in nature. MEK inhibitors have a lower single agent overall response rate, it’s really about 25%. We very rarely see single agent MEK inhibitors. The one where you might see it more is in ocular melanomas, because we do know that MEK inhibitors can work against the GNAQ mutation that we see in ocular melanomas. Side effects are similar to those of BRAF, except that in terms of ocular toxicities, you can see retinal vein occlusion, which leads to blindness. This is something we do not mess around with. You have to permanently discontinue therapy and also retinal pigment epithelial detachments. Have a good ophthalmologist on call when you have these patients on these targeted therapies. In terms of cardiac issues, it’s not QTC, it’s cardiomyopathy that you see with the MEK inhibitors. Generally, one of the unique things with MEK inhibitors is that you see peripheral edema. That’s tough because I just told you that they can get cardiomyopathy. So when you see this peripheral edema, you don’t know if it’s an ejection fraction issue or if it’s just the peripheral edema
from the drug. So you’ve got to sort that out. For management and monitoring, again for ocular, you should ask about it at every visit and permanently discontinue for RVO. For dermatologic, same recommendations as the BRAF inhibitors, in terms of monitoring. Hepatic, also the same as the BRAF inhibitors. Hematologic, we can see some bone marrow suppression with these drugs where you’ll see a little dip in their white count, their red count, and less frequently their platelets. It’s important for patients to be aware of that, and you need to check their complete blood count at each visit. Cardiac-wise, you’ve got to get an echo before you get started, and then if they have any change in their left ventricular ejection fraction, you do need to hold and/or dose reduce.

You are checking echos at one month and then every two to three months thereafter. Generally, they can get some pretty significant diarrhea with these MEK inhibitors. Fortunately, we just talked a lot about diarrhea and the recommendations are the same, you know, dietary modifications, Imodium, Lomotil, things like that. So BRAF plus MEK…you know, we talked about the fact that we can combine ipilimumab with the PD1s and that we see a lot more toxicity there. With BRAF plus MEK we see a lot less toxicity, it’s remarkable. It’s so much better tolerated to give them both together, which is why that’s generally what we do. They are better tolerated and the response rates are higher. The overall response rates for BRAF plus MEK is closer to 60% to 75% depending which study you’re referencing, versus the single agent, 54% for dabrafenib and then the median duration of response is longer. I told you with the single agent BRAF, it’s about six months. When you combine these drugs, it’s about ten
months. The big thing to keep in mind when you combine BRAF and MEK is that they tend to get really high fevers. So you need to do good education on this because your patients are going to end up in the emergency room, and the ER staff is going to work them up for a neutropenic fever, and they are going to be cultured and on antibiotics in no time. And it has nothing to do with infection, it’s just the drug.

So tell them that if they get a fever they should not go to the emergency room, they should call you. Generally, these things can be managed with Tylenol or NSAIDs. You can hold the drug, you can dose reduce. You can get them through the fevers. You can see there that 71% of patients had fevers, so this is something that you’ve got to talk about before you start these therapies. So that brings us to our case studies.

**DR. ANTHONY OLSZANSKI:** Why don’t you go ahead and introduce this one?

**MS. BRIANNA HOFFNER:** All right, so case study number one. We have two. This is a 57-year-old white man who had a history of a T3B, N0, M0 melanoma five years ago and had a wide local excision. He presents to your clinic with mild weight loss and fatigue and right upper quadrant pain. He has a PET/CT scan that shows numerous liver, lung and abdominal metastases. He has a biopsy of the liver, which demonstrates a melanoma similar to the prior. This is an important point whenever you have a patient with new metastatic disease. You should always biopsy a site of metastatic disease to confirm diagnosis, never just assume.
His medical history is fairly noncontributory: hypertension and obesity, a surgical history of appendectomy, family history nothing too big there, and no known drug allergies.

**DR. ANTHONY OLSZANSKI:** So here’s the audience response question. You’ve already been presented the patient. Further work-up or treatment should not include which of the following: Should it not include a brain MRI, not include BRAF mutation status testing, or surgical referral for resection, pain medication, or immunotherapy? Which one would you not do for this particular patient?

**MS. BRIANNA HOFFNER:** I wish we had music.

**DR. ANTHONY OLSZANSKI:** Yes, we need music. You want to sing?

**MS. BRIANNA HOFFNER:** No.

**DR. ANTHONY OLSZANSKI:** No?

**MS. BRIANNA HOFFNER:** You’re welcome.

**DR. ANTHONY OLSZANSKI:** So it looks like the majority of the audience answered right here. We don’t really think that surgical resection for a patient with widely metastatic disease is going to be important, but all the other considerations do need to be something that we keep in mind for this patient. The brain MRI is critical for patients with metastatic melanoma because the brain, even though it is the sanctuary site, is a place where melanoma loves to go. I lost the other ones, but BRAF status is also important. Patients could be treated with a BRAF inhibitor if they are BRAF positive, and certainly a checkpoint inhibitor as well. Want to go through the treatment plan?
**MS. BRIANNA HOFFNER:** Yes. So this patient decided to enroll in a clinical trial and they enrolled in BMS 218, which was looking at ipilimumab at 3 mg/kg in combination with nivolumab at 1 mg/kg. The FDA approved dose of ipi is 3 mg/kg; however, the approved dose of nivo is 2 mg/kg. It’s just important to note the dosing differences in this trial. He received his first cycle on August 13, 2014. On August 20, he called and said that he had a mild rash, so we just managed that symptomatically with supportive treatment, including moisturizing creams, oatmeal baths, and told him to stop taking long, hot showers, which he loved. On that same day, he said that the abdominal pain had already improved. You will remember that he had presented with the abdominal pain and nausea, so just seven days after his first dose those symptoms had already improved. So on August 26, the patient noted changes in his vision. So as I said, this is something we take really seriously. We immediately sent him to Ophthalmology, where he was diagnosed with panuveitis. So this is like the king of all uveitis and this one can actually cause blindness. Whereas, before I said that generally uveitis is treated with a steroid eye drop -- which is true -- this case required oral steroids because of the severity. So he was started on 60 mg of prednisone.

He was seen in clinic on September 6, and his vision had improved, so we started a 3-week taper. Again, we never rapidly taper the steroids. At that visit it’s important to note that his LVH was 206, down from his highest of 586. We use LVH as an important marker in melanoma to help us understand the disease. So the fact that it had dropped that quickly was exciting. On November 25, he had a restaging CT scan of the chest, abdomen and pelvis, and that showed interval
improvement of his metastatic lesions. There were some bilateral ground glass opacities in the lungs, but the patient was feeling very well and had no respiratory symptoms, so we decided to monitor. Unfortunately, on December 2, he developed a dry cough when taking deep breaths, and he came in to clinic. You know we have a very low threshold to bring them in when they have any sort of respiratory symptom. On resting, oxygen was 96%, but when we walked him around it dropped down to 78%.

We got a chest x-ray that showed increased interstitial markings in the periphery of the lungs. If you look on the left there, that’s his baseline in August and then the pneumonitis x-ray on the right in December. You can see those interstitial markings, they’re pretty profound. Sometimes it’s hard to pick up on chest x-ray. Sometimes you do need a CT scan, but this patient was quite obvious. So we admitted him to the hospital. You don’t always have to admit to the hospital, it just depends on the severity of the case and it depends on the patient and their support network. For this patient, we admitted him. We started him on methylprednisolone at 2 mg/kg. He did get a bronch to rule out any infectious issues. That is something that is sort of a plus/minus with pneumonitis. A biopsy of the lung parenchyma was consistent with mild chronic inflammatory changes. He was improved quickly on oxygen and was discharged after two days in the hospital, and started on a four-week steroid taper. The important thing to note here is you have a patient who has injured lungs, who you have now started on high dose steroids, and so they are a set-up for a secondary infection. Please remember with these patients to prophylax against abacterial, fungal or viral
infection in the lungs while you are tapering the steroids. He had a follow-up
chest x-ray that showed improvement and the steroids were tapered over a
month. His symptoms improved, and then he had restaging scans, which showed
extensive progression of disease. Tony, I don’t know if you want to talk about
these PETs?

DR. ANTHONY OLSZANSKI: So this is the PET scan and you can see
the PET scan on the left-hand side shows the extent of his disease. Pretty much
wherever you see black in the visceral organs minus the heart and in the kidneys
and in the bladder, it is all disease. That disease primarily, in this patient, is
centered in the abdomen, a lot of abdominal lymphadenopathy. You can see
remarkable responses, and this is the kind of stuff that we are now seeing in
clinic day after day. A remarkable response, seen on the right, with only the
organs that should be lighting up. No evidence of disease.

MS. BRIANNA HOFFNER: All right. Case study number two.

DR. ANTHONY OLSZANSKI: Let’s talk about this person. And this is a
65-year-old white female with a history of a T4B, that’s an ulcerated deep
melanoma, N1A, M0, stage 3B melanoma. She is status post wide local excision
three years ago and now she presents with enumerable right lower extremity
melanoma lesions. The PET and CT imaging demonstrates no systemic disease,
so she only has what turns out to be intrinsic disease of her leg. BRAF testing,
which is appropriate here shows V600 mutation positive disease. Her medical
history if significant for hypertension, depression, and fibroids, and her surgical
history, as you can see there for lobular carcinoma in situ removed in 2006, and she has an allergy to sulfa drugs.

**MS. BRIANNA HOFFNER:** So –

**DR. ANTHONY OLSANSKI:** You want to go ahead?

**MS. BRIANNA HOFFNER:** No, go for it.

**DR. ANTHONY OLSANSKI:** So audience response question, what is the least appropriate therapy in this patient? Is it not appropriate to initiate BRAF and MEK, or ipilimumab, or isolated limb perfusion, or nivolumab, or to resect or to consider an oncolytic clinical trial. Which one would you not want to do? All right. We have a wandering baseline, but an interesting split here between isolated limb perfusion –

**MS. BRIANNA HOFFNER:** Going down.

**DR. ANTHONY OLSANSKI:** Versus resect those viable lesions. So it can be a little bit confusing here, but I think the right answer here is that you don't want to consider resecting the viable lesions. This patient had innumerable metastatic disease, and it would be impossible to resect all of that kind of disease--impossible. However, isolated limb perfusion, which we did not talk about here, is primarily applying a tourniquet to the leg and infusing high dose chemotherapy. The response rates to that are nearly 70%, even though they are not long lasting. So isolated limb perfusion would be reasonable here, as would really any of the other answers. But resection of all that disease, that's really not going to help this person, and actually is going to make it worse.
**MS. BRIANNA HOFFNER:** Okay. So you want to talk about her treatment plan?

**DR. ANTHONY OLSZANSKI:** So this patient actually elected to enroll in a clinical study, the Amgen 678 study, a phase 1B, phase 2 study investigating talimogene laherparepvec or T-VEC in combination with ipilimumab, and this particular drug we’ll talk a little bit about in a little while. It’s a recombinant oncolytic virus, which is created by modification of the herpes simplex virus. So here we’re injecting patients with HSV. Who thought the day would come when we would inject patients with viruses or bacteria? You might ask yourself that, but in the 1800s Dr. Coley, a surgeon, did this to actually secure some immune responses. So back in the 1800s this was being done with *Staphylococcus*. Unfortunately, that drug wasn’t attenuated and a lot of patients died of infection. We’ve gotten smarter since then, so in this particular drug, it’s an attenuated herpes virus. It also has a gene which encodes a human granulocyte macrophage colony stimulating factor you know and love as GMCSF, and it’s inserted to enhance the anti-tumor immune response. It’s injected into the lesion, and as a caveat here, you have to have a lesion that’s cutaneous, subcutaneous or nodal, and it has to be accessible by either direct examination or through ultrasound.

**MS. BRIANNA HOFFNER:** So this is a picture of one of our patients getting the T-VEC injection. This is a different patient because he’s getting the injection to a posterior auricular lesion here. That’s our radiology nurse and our radiologist who are doing the injections. However, these are injections that can
be done as practice providers, which is important to note. You'll see their outfits there though. This is a biosafety level 2 drug so we gown up, glove up, mask up, and wear the goggles. So the patient receives T-VEC injections on this protocol week one and week four, and then at week six the patient receives both T-VEC and ipilimumab. This trial combines those two drugs. Week eight is just the T-VEC injections and then week nine is just the ipilimumab injections.

DR. ANTHONY OLSZANSKI: So this particular patient developed some hepatitis C. She received the week nine dose of ipilimumab, only two doses on 2/24/2015. Just a few days later was found to have autoimmune hepatitis with ASTs and ALTs, that you can see are well out of the normal range and an LDH was also high. Remember LDH is not only a marker for melanoma, but it’s an acute phase reactant. It will rise in any inflammatory condition, and hepatitis is certainly that. She was given a onetime dose of methylprednisolone and then initiated on a prednisone high dose with labs, then checked biweekly. Remember we taper very, very slowly, so this taper was initiated once the liver tests were within normal limits. Want to talk about her response?

MS. BRIANNA HOFFNER: Yeah. Her response was awesome. Because she had those high liver function tests per protocol, she could not receive any additional doses of ipilimumab. Ipilimumab is generally given for a total of four doses; however, she had only gotten two doses at the time that she developed that autoimmune hepatitis. So the ipilimumab was discontinued, but she did continue to receive the T-VEC injections at week eight and then thereafter she had nothing to inject. She was a complete response. I mean her leg was just
littered – You can’t really see by the pictures, but all the way up to her groin, probably a hundred lesions. We didn’t inject every lesion. That’s an important thing to note about T-VEC is that we have seen some response at lesions that are not the injected lesions. So you can only inject up to 4 mL of this drug per protocol, and the amount that you inject into each lesion is based on the size of the lesion. So for her, we injected a total of eight lesions, but all of her lesions disappeared.

**DR. ANTHONY OLSZANSKI:** So it turns out that T-VEC was also approved by the FDA just last week or so. It’s approved in patients who have failed surgical resection at least once, they have recurrent melanoma and it’s cutaneous, subcutaneous, or nodal disease. It is given as a single agent per FDA guidelines right now, but this trial was in combination. We have other trials in combination, and it’s those particular combination trials that I’m real excited about. So in summary, since 2011 (that’s not that long ago, I can sort of still remember that), a number of therapeutic options that improve overall survival, not just response rate, not just progression free survival, but overall survival, have been approved by the FDA. These include the immunotherapies, the antiCTLA4 ipilimumab and the antiPD1 drugs, nevo and pembro, easier to remember that way, the kinase inhibitors, the BRAF inhibitors, both vemurafenib and dabrafenib, as well as the MEK inhibitor trametinib. We have already seen, as demonstrated in some of the case reports, that we’ve had that some patients can have durable disease control and that has lasted for many, many years. We have some data going back 13 years for ipilimumab for no evidence of recurrent
disease, which is really outstanding and amazing when you think about melanoma. There is a unique adverse event syndrome for all of these agents, and it really does demand both attention and communication—communication with your patients, communication with your medical team. Exciting new therapies are being developed. If there is one thing that we’ve learned in melanoma, it’s that research is the answer. We try to put as many patients on clinical trials as is possible, because while we’ve come a long way since prior to 2011, we still have a long way to go to help the majority of our patients. I think we are going to get there even within our lifetimes, but we have to continue to advance the field. So I really believe that the oncology advanced practitioner plays an important role in the management of patients with this complex disease.

These immune related adverse events and kinase related adverse events, as Brianna has already told you, can be devastating and life threatening. We need somebody there who’s on the ground, who is watching these patients like a hawk, bringing them in when they need to be brought in, and really educating the people who don’t deal with these drugs day in and day out on how to manage these side effects appropriately.

MS. BRIANNA HOFFNER: Absolutely. Because if you catch them early, you can generally get them controlled. So it’s an important piece of it. I think that’s it.

DR. ANTHONY OLSZANSKI: I want to really thank you for your attention.

MS. BRIANNA HOFFNER: Thank you guys for having us, this has been great.
DR. ANTHONY OLSZANSKI: Look at that, we have time for questions.

MS. BRIANNA HOFFNER: Four minutes.

DR. ANTHONY OLSZANSKI: Whoa. Any questions out there?

MS. BRIANNA HOFFNER: I can’t see anything.

DR. ANTHONY OLSZANSKI: Yeah, it’s a little hard.

FEMALE ATTENDEE: Hi. If you’re going to prophylax a patient who’s been hospitalized for a long event against bacterial, what do you usually use, bacterial and viral?

MS. BRIANNA HOFFNER: Good question. So depending on the patient and their status, you know, we might use Levaquin for prophylaxis. We always use Bactrim when we have them on these steroids because really it’s the PCP that you’re most worried about. But depending on how injured the lungs are, you may consider an acyclovir and/or fluconazole. However, with any of the azoles, of course, you would worry about the liver and irritating the liver, and if you have any sort of autoimmune hepatitis, you can have more problems there. So start with Bactrim and looking at the rest of the patient’s case and covering as appropriate from there.

DR. ANTHONY OLSZANSKI: Question over there.

FEMALE ATTENDEE: Yes, I have a question about adjuvant ipilimumab. Now that it’s been approved, would you consider starting it for a patient who had been resected a few months ago, six months ago?

DR. ANTHONY OLSZANSKI: Well, that’s a really good question. I want you to know that the NCCN Panel will be meeting and deliberating on this
question actually quite soon. I think the meeting is on my calendar already for a
couple of weeks away. I think we need to take a really good look at that data. If
you look at the data that has been published so far about adjuvant ipilimumab,
the drug is typically given in the metastatic setting at 3 mg/kg, but in the adjuvant
setting, the study that was done in Europe is a 10 mg/kg dose. Now I want to
stop a minute and talk to you a little bit about drug costs, which we didn’t spend a
lot of time with. Ipilimumab costs about $30,000 per dose at 3 mg/kg. Our
estimated cost on a patient that we are actually starting on that drug with the 10
mg/kg drug right now after mark-up is going to be about $2 million.

**MS. BRIANNA HOFFNER:** $2.6 million, I think.

**DR. ANTHONY OLSZANSKI:** Yeah.

**MS. BRIANNA HOFFNER:** That was their final cost on that, yeah.

**DR. ANTHONY OLSZANSKI:** That’s really outstanding. We do have a
cost issue here. And we have to be careful, because if a patient has a 20% co-
pay, we are looking at over $100,000 that they are responsible for. How many
people here want to sign up for that? Yeah? So the other thing we have to look at
is the actual toxicity in that particular trial. 52% of patients came off of ipilimumab
before they received four doses. In that trial, they also received every-3-month
maintenance doses of ipilimumab. Only 7% of patients completed 3 years of
therapy. Because of the toxicity issue, I think we need to pick our patients very
carefully. If we look at patients with 3A disease, there’s only about a 30% chance
that they are going to die from their disease. There’s a 60% chance that they
have been cured from surgery alone. Ipilimumab at 10 mg/kg has been known to
induce death. On that clinical trial, there were five toxicities that resulted in death that were thought to be drug related. So we have to be very careful in our patient selection. Alternatively, only about 10% of patients with stage 3C disease will be alive five years down the road. So with 3C disease, you are only really putting about 10% of patients at risk because they’re going to die of their disease if you don’t do something. It may be in that patient population that I would consider it. It is FDA approved, however, for any patient with 3B, 3C or resected 4.

**MS. BRIANNA HOFFNER:** Your question about timing there—I don’t know if you want to comment on that too, Tony. You said the patient was resected six months ago. Generally, in the adjuvant setting, we try to initiate an adjuvant therapy within 90 days of resection. Especially with these drugs that are immune therapies that are seeking out that antigen in order to understand how to defend the body from the melanoma. Being so far out from the surgery would probably be, you know, a disservice to the patient in terms of their ability to respond well to that therapy.

**DR. ANTHONY OLSZANSKI:** All right. If there are any other questions, please don’t hesitate to come up to us as we are milling around here. I really want to thank you for your attention today.

**MS. BRIANNA HOFFNER:** Thank you guys.

[END]