Evolving Paradigms in Melanoma Therapy

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## Financial Disclosure (Olszanski)

<table>
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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

Common Types of Cancer

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

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

Murphy K. Janeway’s Immunobiology, 8th Ed. Hamden, CT: Garland Science; 2012.
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
### Immunoediting Hypothesis

<table>
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<tr>
<th>Phase</th>
<th>Description</th>
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<tbody>
<tr>
<td>Elimination phase</td>
<td>• Active immune surveillance may eradicate tumor</td>
</tr>
<tr>
<td>Equilibrium phase</td>
<td>• Balance between elimination and evasion</td>
</tr>
<tr>
<td>Escape phase</td>
<td>• Reduced immunogenicity/enhanced immunosuppression with growth</td>
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Immune Checkpoint Inhibitors

CTLA-4 and PD-1
NCCN Guidelines for Metastatic Disease

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Immune Checkpoints

Anti–PD-1

Anti–CTLA-4

Tumor

T-cell

APC
Anti–CTLA-4 Mechanism of Action

1. Co-stimulation via CD28 ligation activates T cells

2. CTLA-4 ligation down-regulates T-cell responses

3. Blocking CTLA-4 ligation enhances T-cell responses

Upregulation

Downregulation

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

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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<tr>
<td>Arms A vs. C</td>
<td>0.68</td>
<td>.0004</td>
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<tr>
<td>Arms B vs. C</td>
<td>0.66</td>
<td>.0026</td>
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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 “-itises,” 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.
Colitis

- 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,² 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\(^1\) and 14 weeks with anti–PD-1\(^2\)

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

![Graph showing kinetics of adverse events over time (weeks)]

- Rash, pruritus
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

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 (%)

100
90
80
70
60
50
40
30
20
10

Patients Who Died

no./total no.

Median Survival

mo (95% CI)

Nivolumab

Dacarbazine

50/210
96/208

Not reached
10.8 (9.3–12.1)

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 (%)

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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

Vemurafenib vs. Dacarbazine: Best Response

Vemurafenib: 48.4% response

Dacarbazine: 5.5% response

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

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

No. at risk

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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

Response With BRAF + MEK Inhibition

Dabrafenib 150 mg BID + trametinib 2 mg QD

Best unconfirmed response
- Complete response
- Partial response
- Stable disease
- Progressive disease

ORR ~75% vs. 54% BRAF
DoR 10.5 vs. 6 mo

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.
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

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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
Case Study 2: Treatment Plan

- 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.
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.