Stay current on investigational and U.S. Food and Drug Administration-approved immune and molecular-targeted therapies, from common side effects to treatment algorithms. You’ll explore anti-CTLA4 antibodies, anti-PD1 antibodies, and BRAF and MEK inhibitors. Other key topics include CKIT, NRAS-, and CMET-targeted therapies.

**Content Area:** Clinical Practice

**Content Level:** Advanced

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Nothing to Disclose

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Intends to discuss unapproved/investigational use of a commercial product/device during this educational activity. In addition he is a Bristol Myers Squibb & Genetech speaker and received financial support.

**Objectives:**
At the end of this session, participants will be able to:
1. Identify current immune-modulating therapies and immune-related adverse events.
2. Plan treatment algorithms for immune-related adverse events.
3. Evaluate the ability to use molecular-targeted therapies for melanoma treatment based on identified somatic mutations.

**Content Outline:**
1. Overview of melanoma
   A. Types of melanoma
      1. Cutaneous
      2. Mucosal
      3. Ocular

B. Melanoma staging
C. Diagnostic workup
   1. CT and PET scans
   2. MRI brain
   3. CBC, CMP, iron studies
      a. Often elevated LDH
      b. Low iron levels due to vascular nature of tumor
D. Surgery in melanoma
   1. Remains an important treatment option for isolated or life threatening lesions
   2. Important in adjuvant staging for sentinel lymph node biopsies
E. Chemotherapy and biotherapy in melanoma
   1. Still has a role in treatment of metastatic melanoma
   2. Review of common chemotherapy agents
   3. Review of biochemotherapy protocol
   4. High dose IL-2
II. Immune modulating agents and side effects
A. Ipilimumab
   1. Mechanism of action
   2. Efficacy data and dosing considerations
      a. Five-year survival data significantly superior to chemotherapy
      b. Ongoing studies to determine 3 mg/kg versus 10 mg/kg dose
      c. Role of maintenance ipilimumab
      d. Role of ipilimumab re-induction
   3. Side effects
      a. Most commonly rash, diarrhea, hepatitis, and hypopituitarism
      b. Generally managed with topical or systemic steroids
      c. Nursing considerations for early identification and treatment
B. PD1
   1. Mechanism of action
   2. Efficacy data
      a. Phase I studies showing nearly 50% response rates, including patients who did not respond to ipilimumab
   3. Side effects
      a. Rash, diarrhea, hepatitis, hypopituitarism, and pneumonitis
      b. Generally managed with topical or systemic steroids
c. Nursing considerations for early identification and treatment
C. Combinatorial therapies
   1. PD1 plus ipilimumab studies
   2. Ipilimumab or PD1 in combination with molecular targeted therapy agent
III. Molecular targeted therapies
   A. BRAF inhibitors
      1. Immediate tumor reduction with limited duration of efficacy
   B. MEK inhibitors
      1. Used in combination with BRAF therapies to prolong response and decrease side effects
   C. CKIT inhibitors
      1. Commonly used in leukemias; found to have efficacy in CKIT mutated melanomas
   D. Investigational targeted therapies
      1. NRAS inhibitors
      2. CMET inhibitors

Bibliography:
Robert, C., Thomas, L., Bondarenko, I., et al. (2011). Ipilimumab plus dacarbazine for previously untreated metastatic melano-
ma. New England Journal of Medicine, 364, 2517.
Incidence

- Fifth most common cancer (SEER Stat Fact Sheets, 2013)
- 76,690 new cases of Melanoma of the skin in 2013
  - 4.6% of all new cancer cases
  - 1.6% of all cancer deaths
- 921,780 people living with Melanoma of the skin in the United States
- Incidence of melanoma is increasing faster than any other cancer. (American Melanoma Foundation, 2006)
  - 3.8% annual increased incidence in young white women
  - 8.8% annual increase in men 65 and older
  - 2.5% relative yearly increase in children and adolescents

Staging

- AJCC TNM Staging (AJCC, 2010)
  - Stage I
    - Non-ulcerated melanoma 2mm or less in depth
    - No nodal involvement or distant metastases
  - Stage II
    - Ulcerated lesion 2mm or less in depth, or any lesion greater than 2mm in depth
    - No nodal involvement or distant metastases
  - Stage III
    - Any depth of tumor with one or more lymph nodes involved
    - No distant metastases
  - Stage IV
    - Any tumor depth, any number of lymph nodes
    - Distant site of metastases

Ocular Prognosis

- Staging based on size of primary tumor
- DecisionDX-UM (Castle Biosciences, Incorporated)
  - Gene expression profile test that predicts a patient’s risk based on their tumor’s unique biology
  - Risk profile divided into three classes
    - Class 1A: Very low risk, with a 2% chance of the eye cancer spreading over five years;
    - Class 1B: Low risk, with a 21% chance of metastasis over five years; and
    - Class 2: High risk, with 72% odds of metastasis over five years.

Diagnostic Work-Up

- Radiology
  - CT scan, always with IV contrast to assess liver
  - PET scan if needed
  - Always obtain MRI of the brain in stage IV
- Laboratory
  - CBC
  - Leukocytosis with high volume disease
  - Anemia frequently seen
  - CMP
    - LDH often elevated
    - SAIDH with lung/brain metastases
  - Evaluate liver function tests
  - Iron studies
  - Biopsy of metastatic site

Evaluation of Response

- Response Evaluation Criteria in Solid Tumors (RECIST) or modified WHO (mWHO) criteria may not accurately capture tumor responses seen on radiographic imaging after administration of immune therapy
- Immune Related Response Criteria (irRC)
  - Unique response patterns observed with immune therapies (Wolchok, 2009)
    - (a) shrinkage in baseline lesions, without new lesions; (b) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (c) response after an increase in total tumor burden; and (d) response in the presence of new lesions

Adjuvant Therapy

- Interferon only FDA approved therapy
  - High dose interferon IV daily for one month, then SQ three times per week for 11 months
  - Pegylated interferon 6mcg/kg weekly for 8 weeks, then 3mcg/kg weekly for weeks 9-252
- Clinical trials
  - Immune therapies
  - Targeted therapies
  - Vaccine therapies
Chemotherapy, Biochemotherapy & IL-2

- Common chemotherapy regimens
  - Carboplatin/Paclitaxel
  - Carboplatin/Abraxane
  - Abraxane/Auxtin
  - DTIC
  - Temodar
- Biochemotherapy
  - Interleukin, Interferon, Temodar, Vincristine, Cisplatin
  - Five day inpatient regimen
- High Dose IL-2
  - IL-2 (Proleukin, Aldesleukin) is a T-cell growth factor with potent anti-tumor activity.
  - Significant side effects include hypotension, vomiting, diarrhea, confusion, oliguria, thrombocytopenia, fever/chills and malaise
  - Response rate 12.5-16%

Immunotherapy for Cancer (Melanoma)

- Immunotherapy is quickly becoming a viable way of inducing durable responses in many cancers.
- Tumors have several ways to suppress and evade the immune system:
  - Induction of tumor-infiltrating regulatory T-cells
  - Signaling defects causing a reduced T-cell proliferation
  - Suboptimal antigen presentation due to down-regulation of MHC class 1 molecules or absence of co-stimulatory molecules
  - Compromised cell mediated cytotoxicity of tumor-infiltrating lymphocytes
  - High levels of tolerogenic molecules within the tumor

Ipilimumab (anti-CLTA-4)

- Anti-CTLA-4 Therapy Rationale
  - Activation of cellular immunity begins when a T-cell recognizes peptide fragments of intracellular proteins that are expressed on the surface of antigen presenting cells (APC) bound to specific mixed histocompatibility complex (MHC) modules.
  - Requires presence of co-stimulatory molecule B7 and results in up regulation of CTLA-4.
  - The CTLA-4 receptor on the T lymphocytes is a negative regulator of T cell activation that binds to B7 with a higher affinity than CD28 on the antigen presenting cell. This is the physiologic “brake” on an activated immune system.
  - Ipilimumab (Yervoy®, Bristol-Myers Squibb) is a fully-human monoclonal antibody to CTLA-4 and can prevent this feedback inhibition resulting in an immune response against the tumor.
  - It is this same mechanism that can lead to potentially severe or life threatening autoimmunity, or immune-mediated, adverse events.

Ipilimumab Response Rates

- The anti-tumor effects mediated by CTLA-4 blockade has been attributed to sustained active immune response against cancer cells.
- Large phase II study 676 patients randomly assigned in a 3:1 ratio to ipilimumab plus a glioblastoma vaccine, dacarbazine alone, or dacarbazine (Robert, 2004)
  - OS significantly increased in patients receiving ipilimumab (10mg/kg) vs placebo in gp100 (gp100
  - Survival benefit was not restricted to particular subcutaneous sites at presentation, prior therapies.
  - Objective response rate significantly improved with ipilimumab 0-1% in 3:1 randomization arm vs 1.6% in the control arm.
  - When all objective partial or complete response was observed, they appear to be durable.
- Subset of 25 patients (30) with metastatic melanoma randomly assigned to ipilimumab (10mg/kg) plus dacarbazine (800mg/m²) vs placebo plus dacarbazine (Robert, 2011)
  - Dacarbazine alone or placebo without ipilimumab achieved 11.2mos in IPMNs in the placebo plus dacarbazine arm.
  - Long-term duration of response. Recent data from NIH representing 177 patient treated on 3 different studies between 2002-2008 showed that 5% of these patients experienced a complete response and 10% surviving 5 years or better of follow-up. In some cases, though, the responses were delayed, even up to 30 mos. The most frequent complete responses were in patient who received 6-2 with ipilimumab (Prints, 2012).

Ipilimumab Administration

- Locally advanced or un-resetable stage III melanoma or stage IV metastatic melanoma.
- 3 mg/kg IV q3w x 4
- Administered over 90-minutes, infusion reactions rare, no premedication required.
- Labs, including CMP and Thyroid Panel should be checked at baseline and before each dose.

Ipilimumab Side-Effects

- “immune-mediated or immune-related toxicity or adverse events (IMAEs)”
  - While a wide variety of toxicities have been reported, the most common are:
    - Enterocolitis
    - Hepatitis
    - Dermatitis
    - Endocrinopathies
  - Toxicity generally occurs several weeks into therapy and 10-15% of pts receiving ipilimumab experienced a severe or life-threatening (gr 3 or 4) toxicity.
  - Prompt medical attention, treatment interruption, and early administration of corticosteroids are essential for management of IMAEs.
Programmed death 1 (PD-1)

- Programmed death 1 (PD-1) protein is another T-cell coinhibitory receptor with a structure similar to CTLA-4 with a distinct biologic function and ligand specificity.
  - 2 known ligands – PD-L1 (B7-H1) and PD-L2 (B7DC).
  - Different from CTLA-4, PD-L1 is selectively expressed on many tumors.
- PD-1 binds to its ligand (PD-L1 which is often present on tumor cells) and the ability of the activated T cell to produce an effective immune response is down-modulated.
- Antibodies directed against PD-1 (nivolumab, MK-2475) or the PD-1 ligand (MPDL-3280, MEDI 4332) may restore or augment an antitumor response and are actively being studied in numerous on-going clinical trials.

Anti-PD1/L1 Response Rates

- Nivolumab (anti-PD-1)
  - Phase II trial with 107 melanoma patients. Overall objective response rate 31% and additional 7% had stable disease, median duration of response was 24 mos; median OS was 17 mos, 43% alive at 2 years (Sznol, 2013).
  - Another study looking at different doses of nivolumab had an objective response rate of 22%.
- MK-3475 (anti-PD-1)
  - Nonrandomized study treating 135 patients with advanced melanoma at different doses and dosing schedules, overall response rate was 37%, but the 10mg/kg q2w schedule had the highest with 50% response rate. Median progression free survival was greater than 7 mos (Hamid, 2013).
- MPDL-3280 (anti-PD-L1)
  - Phase 1 dose escalation study with 45 patients with advanced melanoma, overall response rate was 29% (Hamid, 2013).

Anti-PD-1/L1 Toxicity

- Nivolumab
  - Grade 3 or 4 AEs’s seen in 9-14% of patients depending on study (Sznol, 2013; Sznol, 2013, Wolchok, 2013).
  - Variety of autoimmune side effects seen, toxicity appeared less frequently than with ipilimumab.
  - Most commonly observed events include:
    - Pneumonitis
    - Colitis
    - Hypothyroidism
    - Hepatitis
    - Hypertension
  - Infusion reactions observed about 10% of the time, mostly at the 10mg/kg dose level (Sznol, 2013).
  - All infusion reactions were grade 1 or 2 with exception of 1 grade 3 reaction.
  - Severe adverse events occurred in only 2% of patients (Hamid, 2013, Sznol, 2013, Wolchok, 2013).

Combination Immunotherapy for Advanced Melanoma

- Anti-CTLA-4 and Anti-PD-1 appears to have a higher level of anti-melanoma activity than either agent alone (Wolchok, 2013).
  - Results of a phase 1 trial
    - 53 patients with advanced melanoma, 40% had an objective response, with 16/21 having an 80% or greater reduction in tumor burden.
    - Clinical activity seen in 65% of patients.
    - Concurrent anti-CTLA-4 and anti-PD-1 resulted immune-mediated adverse events observed in 93% of cases – high but manageable.
      - Most common severe AEs: hepatotoxicity 15%, GI 9%, renal toxicity 6%
    - Severe toxicity noted in 49% and treatment was discontinued in 21%.
  - Current on-going trial comparing the combination of nivolumab plus ipilimumab vs either checkpoint inhibitor as a single agent underway (CA209-067)

Other combinations

- Ipilimumab plus GM-CSF- ECOG 1608
  - Studied by ECOG, 245 patients randomly assigned to ipilimumab alone at 10mg/kg vs ipilimumab plus GM-CSF.
  - No difference in response rate, but overall survival was significantly improved with the addition of GM-CSF (17.5 vs 12.7 mos) (Hodi, 2013).
  - Addition of GM-CSF also resulted in lower incidence of high grade adverse events.

Other Immune Regulatory Checkpoints

- Antibodies targeted against a number of other regulatory checkpoints are being evaluated.
  - Examples include 4-1BB (CD137) and OX40.
General Guidelines for Treating IMAE’s from immunotherapy

- Rule out all causes of adverse event, and if no other explanation, assume IMAE.
- Consider symptomatic care when appropriate.
- Consider holding or delaying a dose for mild toxicity.
- Use steroids when necessary – not too early, not too late.
- Moderate dose steroids for moderate toxicity, high doses for more serious toxicity. May need to add adjuvants to steroids if toxicity appear refractory, i.e. infliximab or mycophenolate.
- When steroids are used for serious toxicity, taper over at least 30 days. Rapid taper may result in recurrence or toxicity and may be more severe.

Immune Mediated Colitis

- Diarrhea and/or colitis is the most common and potentially most serious complication of anti-CTLA-4 therapy.
  - Some trials report up to 31% of patients experiencing some grade of diarrhea, with 6% experiencing severe colitis (Hodi, 2010).
  - Bowel perforation, sepsis, and death have been reported.
  - Close monitoring is required to prevent progression to more serious complications.

Immune Mediated Colitis

Symptom Surveillance

- Signs and symptoms to monitor for: diarrhea, abdominal pain, nausea, inability to eat or drink, mucus or blood in the stool.
- Median time to onset from first dose 6-7 weeks from first dose (Hodi, 2010).
- 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 clostridium difficile or other infections diarrheas.
- Clinical Pearl – colitis can occur without diarrhea, important to take all GI-related symptoms seriously and evaluate.

Immune Mediated Colitis

Symptom Management

- MILD/Gr 1 – less than 4 stools per day above baseline – manage symptomatically, i.e. bland diet, PPI, immodium/lomotil, consider delaying a dose until sx improve.
- MODERATE/Gr 2 – increase of 4 to 6 stools per day above baseline – colonoscopy indicated and treatment with steroids should be initiated. Low-dose steroids may be sufficient 0.5mg/kg per day of solumedrol or equivalent – but if no improvement within 24 hrs would consider higher dose. Hold infliximab.
- SEVERE/Gr 3 or higher – increase of 7 or more stools per day above baseline or other complications – initiate high dose steroids 1mg/kg of solumedrol or equivalent. Infliximab should be discontinued. For patients who do not respond to high doses steroids within 1 week or show clinical signs of worsening colitis, consider infliximab.
- Prevention – no known methods. Budesonide was tested as a way to prevent immune-related colitis and a randomized phase II trial no benefit shown (Weber, 2009).

Immune Mediated Hepatitis

- Less common than colitis, seen in 2 to 9% of patients and at least 1 death has been reported on anti-CLTA-4 therapy alone (Hodi, 2010).
- Hepatotoxicity appears worse when ipiliimumab combined other drugs including dacarbazine (Robert, 2011), vemurafenib (Ribas, 2013), and anti-PD-1 (Wolchok, 2013) and should be used cautiously.

Immune Mediated Hepatitis

Symptom Surveillance

- Hepatic function (transaminases and total bilirubin) should be monitored at baseline and prior to each dose of treatment.
- Abnormal LFT’s should be monitored more frequently.
Immune Mediated Hepatitis
Symptom Management
• Rule out other causes of liver function test abnormalities.
• Increase LFT monitoring until improvement.
• Corticosteroid treatment should be used with Gr 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.

Immune Mediated Dermatitis
Symptom Surveillance
• Determination of severity and treatment is driven by symptoms.
• Rule out other etiologies of rash, i.e. poison ivy, contact dermatitis, cellulitis, etc.
• Rash is generally not thought of as an infusion-related event.

Immune Mediated Dermatitis
Symptom Management
• Commonly seen with anti-CTLA-4 with up to 40% of patients reporting some grade of dermatologic side effect (Hodi, 2010).
  – Occasionally see severe rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, full thickness dermal ulceration)
  – Median time to onset for moderate to severe dermatologic toxicity was 3 weeks (Hodi, 2010).

Immune Mediated Endocrinopathies
Symptom Management
• 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 prior to each dose. 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 (Hodi, 2010).

Immune Mediated Endocrinopathies
Symptom Surveillance
• A variety of autoimmune endocrinopathies have been reported (Corsello, 2013) with ipilimumab 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 has all been reported.
• Mechanism of injury not fully understood.
Immune Mediated Endocrinopathies
Symptom 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 stable and at less than 7.5mg of prednisone, then treatment can be continued.
- Clinical Pearl – Does a pre-existing thyroid disorder put patient at higher risk of developing additional endocrinopathies? Not as far as we know.

Other IMAEs

- Long list of other IMAEs
  - Ocular manifestations – conjunctivitis, uveitis and scleritis
  - Pneumonitis
  - Neurologic complications – Gillian Barre syndrome, inflammatory myopathy, aseptic meningitis, temporal arteritis, posterior reversible encephalopathy syndrome.
  - Sarcoidosis.
  - Systemic vasculitis, including renal disease.
  - Autoimmune pancreatitis.
  - Red cell aplasia, pancytopenia, autoimmune neutropenia, acquired hemophilia A.

Molecular Mutations in Melanoma

- Numerous targeted therapies derived from the Ras-Raf-MEK-ERK signaling pathway
  - BRAF inhibitors for V600 mutations
  - MEK inhibitors for BRAF or NRAS mutated melanomas
- C-KIT mutations
- CMET mutations
- GNA-Q and GNA-11 in Ocular Melanoma

Testing for Molecular Mutations

- Comprehensive molecular testing should be done on all melanomas
  - Some testing can be done at local or hospital based laboratories
  - Organizations including Caris Life Sciences or FoundationOne
- BRAF Testing
  - Sanger Sequencing
  - Cobas™ 4800 BRAF Mutation test
    - 20% more accurate than Sanger Sequencing with fewer false negatives and invalid results

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 Inhibitors

- Two FDA approved BRAF Inhibitors:
  - Vemurafenib (Zelboraf™, Genentech)
  - Dabrafenib (Tafinlar™, GSK)
- Side effects
  - Dermatologic
    - Potential for severe photosensitivity
    - Squamous cell carcinoma, keratoakanthosis, new melanomas
  - Ocular
    - Retinopathy
  - Cardiac
    - QTc prolongation
  - Hepatic
    - Transaminitis or increased bilirubin
  - General
    - Diaphoresis
    - Joint pain
    - Nausea
    - Fatigue
BRAF Inhibitor Side Effect Management/Surveillance

- **Dermatologic**
  - (Melanoma clinical trial, 15 days after starting therapy, monthly for the first three months, then every three months thereafter; 60% with grade 1 rash, 23% grade 2 rash, 5% grade 3 rash, 1% grade 4 rash) (45%)
  - Treatment may continue with dose reduction: dose reduction to grade 1, with reinitiation of therapy

- **Ocular**
  - Monitor for visual symptoms at each clinic visit
  - Dose reduction for severe visual effects

- **Cardiac**
  - Benefit of prevention of therapy: 15 days after starting therapy, monthly for the first three months, then every three months thereafter

- **Hepatic**
  - Monitor liver function tests at least monthly during therapy

- **Dermatologic**
  - Acneiform dermatitis
  - Medications with less risk: selumetinib: hydrophilic, 160 mg orally daily in 4 divided doses

- **Ocular**
  - Retinal toxicity (58%)

- **Hematologic**
  - Transaminitis

MEK Inhibitors

- **Trametinib (MEK1/2 inhibitor)**
- **Side effects:**
  - Ocular
  - Cardiac
  - Dermatologic
  - Hematologic

MEK Inhibitor Side Effect Management/Surveillance

- **Ocular**
  - Permanently discontinue therapy for patients with retinal vein occlusion

- **Cardiac**
  - Benefit of preinitiation therapy: 15 days after starting therapy, monthly for the first three months, then every three months thereafter

- **Dermatologic**
  - Rash
  - Arthralgia

- **Hematologic**
  - Anemia

- **Other**
  - Fatigue

BRAF plus MEK

- **Combination therapy with Dabrafenib and Trametinib approved in January 2014**

- **Side effects reported in Phase I/II study:**
  - Fever (71%)
  - Chills (58%)
  - Fatigue (53%)
  - Rash (45%)
  - Nausea (44%)
  - Vomiting (40%)
  - Decreased appetite (22%)
  - Constipation (22%)

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

C-KIT Mutations

- **Most commonly occur in acral or mucosal melanomas**
- **Imatinib mesylate (Gleevec™, Novartis Pharmaceuticals)** is a selective inhibitor targeting C-KIT
- **Phase II trial of Imatinib mesylate in c-KIT melanomas (Carvajal, 2011):**
  - Overall response rate of 23.3%, with tumor regression in 41.3% of patients
  - Side effects include edema, fatigue, anorexia, nausea, elevated AST/ALT

Combinatorial Therapy

- **Opportunity to attain immediate decrease in tumor burden from BRAF-inhibition and long term response from immunotherapy**
- **Anti PDL1/PD1 + BRAF-inhibitor**
  - Genentech clinical trial investigating anti-PD1 + Vemurafenib (NCT01656642)
  - Initial both drugs administered concurrently with Grade 3/4 rash and liver function abnormalities
  - Protocol amended for patients to receive BRAF monotherapy for two months, followed by initiation of anti-PD1
- **Yervoy + BRAF-inhibitor**
  - Both drugs commercially available
  - Increased liver toxicity when administered concurrently (zeleral.com)
Future Directions

- Antibody drug conjugates
- Radiation therapy with immunotherapy
- Combined immunotherapies
- Immunotherapy and targeted therapy
- Adoptive/Adaptive T-Cell Therapy

Summary

- Incidence of melanoma increasing faster than any other cancer and remains a challenging disease to treat (American Melanoma Foundation, 2006)
- Rapidly evolving therapies with improved and durable outcomes
  - Yervoy overall response rate 13% (Hodi, 2010)
  - Anti-PD1 best overall response rate nearly 50% (Hamid, 2013)
- Oncology nurses need to be knowledgeable about immune related adverse events and appropriate management
- Increasing identification of molecular targets for actionable therapies
  - BRAF, NRAS, CMET, c-KIT,