Ask the Experts: Practice Pearls for Immunotherapy in Advanced Melanoma

Presented as a Live Webinar

Tuesday, February 16, 2016
12:00 p.m. – 1:00 p.m. ET

On-demand Activity
Live webinar recorded and archived to be watched at your convenience
Available May 16, 2016

www.cemidday.com/15-melanoma/experts

This activity is sponsored by the American Society of Health-System Pharmacists (ASHP) and planned by ASHP Advantage, a division of ASHP.

Supported by an educational grant from Merck

Ask the Experts: Practice Pearls for Immunotherapy in Advanced Melanoma

Activity Overview

This activity will focus on current issues related to the use of immunotherapy in patients with melanoma. The faculty will address key issues and provide practice pearls for physicians and pharmacists.

The content for this activity is based on questions and comments from participants in a recent educational symposium on this topic. Time for questions from the webinar audience will be provided at the end of the presentation.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Describe the indications, administration, and safety precautions for the use of oncolytic vaccines in advanced melanoma.
- Using patient case-based scenarios compare the use of interferon versus ipilimumab in the adjuvant setting, including patient selection, toxicity monitoring and management.
- Discuss the challenges of drug access, including patient assistance programs and emerging value metrics in immuno-oncology.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit.

Live Activity ACPE #: 0204-0000-16-419-L01-P

On-Demand Activity ACPE #: 0204-0000-16-419-H01-P

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The American Society of Health-System Pharmacists designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants will process CE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CE credit must be claimed no later than 60 days from the date of the live activity or completion of a home study activity.

Webinar Information

Visit www.cemidday.com/15-melanoma/experts to find:

- Webinar registration link
- Group viewing information and technical requirements
- CE webinar processing information

Additional Educational Activities in this Initiative

- This live activity will be archived and offered as web-based on-demand learning at www.cemidday.com
- A web-based activity based on the 2015 Midyear Clinical Meeting "Emerging Therapies for the Treatment of Advance Melanoma: Focus on Immunotherapy" (1.5 hours of CE, please note that individuals who claim CE credit for the live symposium or webinar are ineligible to claim credit for the web-based activities)

Activity Faculty

Christine M. Walko, Pharm.D., BCOP, FCCP, *Activity Chair*
Personalized Medicine Specialist
DeBartolo Family Personalized Medicine Institute, Moffitt Cancer Center
Associate Professor
USF School of Medicine
Tampa, Florida

Christine M. Walko, Pharm.D., BCOP, FCCP, is Clinical Pharmacogenetics Scientist at the DeBartolo Family Personalized Medicine Institute and Clinical Scientist in the division of population science at the H. Lee Moffitt Cancer Center and is also Associate Professor at the University of South Florida Morsani College of Medicine in Tampa, Florida. She is also Co-Chair of the Clinical Genomics Action Committee (CGAC) at H. Lee Moffitt Cancer Center. Dr. Walko received her Doctor of Pharmacy degree from Duquesne University in Pittsburgh. She completed a pharmacy practice residency at Virginia Commonwealth University Health System/Medical College of Virginia Hospitals in Richmond, Virginia. She also completed a hematology/oncology specialty residency at the University of North Carolina (UNC) Hospitals and Clinics and a hematology/oncology fellowship at the University of North Carolina School of Pharmacy in Chapel Hill, North Carolina. She is a board-certified oncology pharmacist.

Prior to her current position, Dr. Walko was Clinical Assistant Professor, Division of Pharmacotherapy and Experimental Therapeutics in the Institute of Pharmacogenomics and Individualized Therapy at the University of North Carolina Eshelman School of Pharmacy and Director of the Clinical Trial Unit Clinical Pharmacology Lab at the North Carolina Cancer Hospital at University of North Carolina Hospitals and Clinics Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Dr. Walko is a member of ASHP and is a fellow of the American College of Clinical Pharmacy (ACCP) and has served as Oncology PRN president elect and secretary/treasurer for ACCP. She is also a member of the Hematology and Oncology Pharmacists Association (HOPA), the American Society of Clinical Oncology (ASCO) and the North Carolina Oncology Pharmacists Association. Dr. Walko has also served as president and secretary/treasurer at the Triangle College of Clinical Pharmacy. She serves on the International Society of Geriatric Oncology (SIOG) Task Force on Oral Cytotoxic Chemotherapy Dosing in the Elderly and is faculty for the Global Resource for Advancing Cancer Education (GRACE). Dr. Walko has received the teacher of the year award at the UNC Eshelman School of Pharmacy multiple times.

She has conducted research and published extensively in oncology therapy and presented nationally and internationally on oncology, pharmacogenomics, and other topics related to treating patients with cancer.

Ask the Experts: Practice Pearls for Immunotherapy in Advanced Melanoma

Morganna Freeman, D.O., FACP
Chief Medical Oncology Fellow
H Lee Moffitt Cancer Center & Research Institute
Tampa, Florida

Morganna Freeman, D.O., FACP, is Chief Medical Oncology Fellow at H. Lee Moffitt Cancer Institute, a National Cancer Institute and National Comprehensive Cancer Network member institution.

Dr. Freeman obtained her undergraduate degree in biology from St. Mary's University in San Antonio, Texas. After graduation, she worked as a certified clinical research coordinator before entering medical school at Lake Erie College of Osteopathic Medicine. She completed her internship and residency in internal medicine at the University of Florida in Gainesville, Florida. As Chief Resident, her interests in education and health policy flourished. Dr. Freeman received her medical oncology fellowship training at H. Lee Moffitt Cancer Institute where she has spent the majority of her fellowship under the mentorship of Dr. Jeffrey Weber M.D., Ph.D., an internationally-recognized expert in melanoma and immunotherapy.

Dr. Freeman has frequently collaborated with Dr. Weber on melanoma immunotherapy research, and recently presented the results of their work at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting. In addition to her academic accomplishments, Dr. Freeman has participated in the ASCO/American Association for Cancer Research Methods in Clinical Cancer Research workshop, holds National Institute of Health and Collaborative Institutional Training Initiative (CITI) certifications in clinical research, and has served numerous physician organizations in positions of leadership.

Disclosure Statement

In accordance with the Accreditation Council for Continuing Medical Education's Standards for Commercial Support and the Accreditation Council for Pharmacy Education's Standards for Commercial Support, ASHP requires that all individuals involved in the development of activity content disclose their relevant financial relationships. A person has a relevant financial relationship if the individual or his or her spouse/partner has a financial relationship (e.g. employee, consultant, research grant recipient, speakers bureau, or stockholder) in any amount occurring in the last 12 months with a commercial interest whose products or services may be discussed in the educational activity content over which the individual has control. The existence of these relationships is provided for the information of participants and should not be assumed to have an adverse impact on the content.

All faculty and planners for ASHP Advantage education activities are qualified and selected by ASHP and required to disclose any relevant financial relationships with commercial interests. ASHP identifies and resolves conflicts of interest prior to an individual's participation in development of content for an educational activity. Anyone who refuses to disclose relevant financial relationships must be disqualified from any involvement with a continuing pharmacy education activity.

- All faculty and planners report no financial relationships relevant to this activity.

CE IN THE MIDDAY

Ask the Experts: Practice Pearls for Immunotherapy in Advanced Melanoma

Christine M. Walko, Pharm.D., BCOP, FCCP, *Activity Chair*
Personalized Medicine Specialist
DeBartolo Family Personalized Medicine Institute, Moffitt Cancer Center
Associate Professor, USF School of Medicine
Tampa, Florida
Morganna Freeman, D.O., FACP
Chief Medical Oncology Fellow
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida

This activity is sponsored by the American Society of Health-System Pharmacists (ASHP) and planned by ASHP Advantage, a division of ASHP.
Supported by an educational grant from Merck
1.0 hr. CE

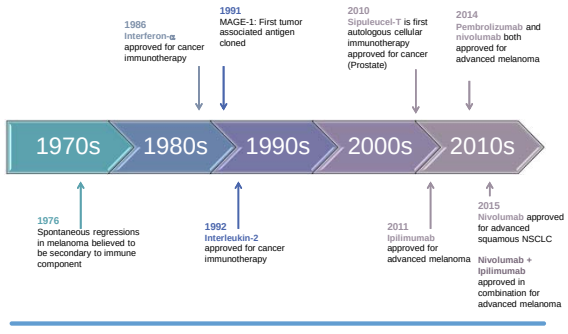
Disclosures

- All faculty and planners report no financial relationships relevant to this activity.

Objectives

- Describe the indications, administration, and safety precautions for the use of oncolytic vaccines in advanced melanoma.
- Using patient case-based scenarios, compare the use of interferon vs. ipilimumab in the adjuvant setting, including patient selection, toxicity monitoring and management.
- Discuss the challenges of drug access, including patient assistance programs and emerging value metrics in immuno-oncology

Progression of Immunotherapy



Progression of Immunotherapy 2015

- **Ipilimumab** approved for adjuvant therapy of cutaneous melanoma following complete resection
- Combination **ipilimumab** and **nivolumab** approved for advanced melanoma
- **Nivolumab** and **pembrolizumab** approved as first-line therapy for advanced melanoma
- **Talimogene laherparepvec** ("T-VEC") approved for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

History of Immunotherapy

	Interleukin-2	Ipilimumab	Nivolumab Pembrolizumab
Immune target	Nonspecific T-cell growth factor	CTLA-4	PD-1
Approximate number of patients with ≥grade 3 toxicities	85%	26%	15%
Classic toxicities	Capillary leak syndrome with hypotension, fever, headache, myalgias, diarrhea, liver toxicity,	Rash, diarrhea/colitis, liver toxicity, endocrine toxicity	Rash diarrhea, liver toxicity, endocrine toxicity

CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4, PD-1: Programmed Death Receptor 1

Petrella T et al. *Cancer Treat Rev*. 2007; 33:484-96.
Horvat T et al. *J Clin Oncol*. 2015; 33:3193-8. Larkin J, et al. *N Eng J Med*. 2015; 373:23-34.

Patient Case #1

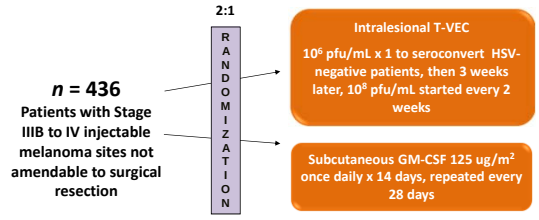
- PR is a 48-year-old male with newly diagnosed, locally advanced melanoma involving several lesions on his forearm
- He is about to begin therapy with TVEC
- The family asks about risk of viral transmission following administration and if any special precautions should be taken

Talimogene Laherparepvec (T-VEC)

- Herpes simplex virus (HSV) type-1 derived oncolytic virus
  - Selectively replicates in tumor cells → Cell lysis
- Modifications:
  - Deletion of *ICP34.5*: decreases viral pathogenicity and increases tumor-selective replication
  - Deletion of *ICP47*: decreases virally mediated antigen presentation suppression and increases expression of the HSV *US11* gene
  - Engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF) to increase cancer immunity
- FDA Approval: **October 27, 2015**
  - local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

Andtbacka RH et al. *J Clin Oncol.* 2015; 33:2780-8.

Phase III T-VEC vs. GM-CSF



- **Primary endpoint:** Durable response rate (DRR) defined as objective response lasting continuously ≥6 months per independent review.
- **Exclusions included:** patients with more than 3 visceral metastatic sites (except lung or nodal) and those requiring intermittent or chronic antivirals (e.g., acyclovir) or high-dose steroids. Patients with autoimmune disease **NOT** requiring high dose steroids **WERE** eligible.

pfu=plaque forming unit

Andtbacka RH et al. *J Clin Oncol.* 2015; 33:2780-8.

Phase III T-VEC vs. GM-CSF: T-VEC Dosing

Lesion size (cm)	Injection volume	Dose (concentration of 10^6 pfu/mL)
>5	Up to 4 mL	Up to 4 million pfu
>2.5 - 5	Up to 2 mL	Up to 2 million pfu
>1.5 to 2.5	Up to 1 mL	Up to 1 million pfu
>0.5 to 1.5	Up to 0.5 mL	Up to 500,000 pfu
≤0.5	Up to 0.1 mL	Up to 100,000 pfu

Maximum of 4 mL total volume across all lesions per visit

Andtbacka RH et al. *J Clin Oncol.* 2015; 33:2780-8.

Phase III T-VEC vs. GM-CSF

	T-VEC	GM-CSF	P-value
Durable response rate	16.3%	2.1%	<0.001
Overall response rate	26.4%	5.7%	Not available
Complete response rate	10.8%	<1%	<0.001
Overall survival	23.3 months	18.9 months	0.051

- Responses were seen in both injected and uninjected lesions
- Of the 78 patients responding to T-VEC, 54% initially met criteria for disease progression before experiencing a response
- Adverse effects were manageable with the most common being chills, pyrexia, injection site pain, nausea, flu-like illness and fatigue

Andtbacka RH et al. *J Clin Oncol.* 2015; 33:2780-8.

T-VEC Summary

- T-VEC is the first oncolytic immunotherapy vaccine to show therapeutic benefits in melanoma
- Responses were higher in previously untreated patients, or those with skin, subcutaneous or nodal only disease
  - Patients with Stage IIIB/IIIC disease had the greatest benefit followed by Stage IVM1a
- Treatment was well-tolerated

Preparation Instructions

- How supplied
  - 1 x 10^6 (1 million) pfu/mL (**light green** cap)
  - 1 x 10^8 (100 million) pfu/mL (**royal blue** cap)
  - No preservative, store -90 °C to -70 °C
  - Thaw and prepare immediately prior to administration

Risk of Viral Shedding

- Modifications:
  - Deletion of *ICP34.5*:
    - Associated with neurovirulence
    - Decreases viral pathogenicity and increases tumor-selective replication
  - Deletion of *ICP47*:
    - Associated with antigen presentation allowing wild type HSV1 to escape detection by the immune system
    - Decreases virally mediated antigen presentation suppression and increases expression of the HSV *US11* gene

NCT 02014441: Viral Shedding Study

- Phase II, Multicenter, single arm trial to evaluate the biodistribution and shedding of T-VEC in unresectable, Stage IIIB to IVM1c melanoma
- Primary endpoint:
  - Detectable TVEC DNA in blood and urine anytime following administration within first 3 cycles
- Secondary endpoints include:
  - Rate of detection of DNA from dressings, surface of injected lesions, oral mucosa swabs and genital swabs during and following treatment
  - Response rates and safety
- Study completed enrollment but evaluation is still ongoing

FDA Combined CTGTAC and ODAC Meeting, 4/29/2015 Presentation.

NCT 02014441: Viral Shedding Study

- Preliminary findings from 20 of the 40 patients treated
  - Viral shedding occurs at injection-site and passes through the dressing
  - DNA was cleared in 93% of patients before the next injection and was found in the urine on the day of in the injection
  - No DNA found in the oral mucosa during the 4 cycles on study or from 7 herpetic lesions found on study subjects

FDA Combined CTGTAC and ODAC Meeting, 4/29/2015 Presentation.

Conclusions and Patient Recommendations

- Precautions
  - Highest chance of viral transmission is with direct contact to the injection site or dressing
  - Blood should be considered potentially infectious
  - Urine can be infectious on the day of the injection
- Patient recommendations
  - Avoid direct contact with treatment sites, dressings or body fluids
  - Wear gloves when changing dressings and keep treatment sites covered for at least one week following treatment
  - Dispose of all used dressings and cleaning materials in a sealed plastic bag before throwing in the garbage

Ongoing Clinical Trials

- Neoadjuvant T-VEC plus surgery vs. surgery alone
- Combination trials
  - Pembrolizumab with or without T-VEC
  - Ipilimumab with or without T-VEC
- Biomarker focused trial on immune response
- Viral shedding trials
  - Total of 60 patients with expected results in late 2016
  - Total of 920 patients and close contacts (ends in 2024)
- Role in other disease states
  - Sarcoma, head and neck cancer, hepatocellular carcinoma

Clinicaltrials.gov (accessed 2016 Jan 6).

Which of the following is FALSE regarding T-VEC?

a. The dose administered is based on the size of the lesion(s) being injected.
b. Doses may be prepared up to 24 hours prior to injection.
c. Immunosuppressed contacts are at risk of HSV1 infection if they touch the patient's occlusive dressing.

CE IN THE MIDDAY

Morganna Freeman, D.O., FACP
Chief Medical Oncology Fellow
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida

ashp

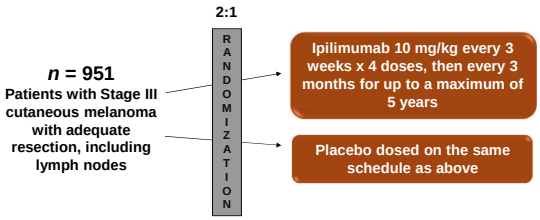
Patient Case #2

- BT is a 63-year-old female with a 2 mm thick, ulcerated melanoma found on the left forearm. Sentinel node sampling was positive for metastatic involvement. Axillary dissection was negative for distant spread.
- Final pathology: T3bN1b (Stage IIIc)
- She wants to know what treatment options are available for adjuvant therapy

Which adjuvant treatment option would you recommend for this Stage IIIc melanoma patient?

a. Ipilimumab 10 mg/kg
b. Ipilimumab 3 mg/kg
c. Interferon alfa-2B
d. No adjuvant therapy

EORTC 18071: Adjuvant Ipilimumab



- **Primary endpoint:** Recurrence free survival as assessed by an independent review committee
- **Secondary endpoints**: distant-metastatic free survival, overall survival, toxicity profile and quality of life (assessed by the QLQ-C30)

Eggermont AM, et al. *Lancet Oncol.* 2015; 16:522-30.

EORTC 18071: Adjuvant Ipilimumab

- Comparison of ipilimumab with placebo in 951 patients with completely resected Stage III melanoma
- Primary endpoint: median recurrence free survival
  - Ipilimumab: 26.1 months
  - Placebo: 17.1 months

  HR 0.75, p=0.0013
- Grade ≥3 Toxicity: 5 treatment-related deaths due to ipilimumab
  - 16% gastrointestinal
  - 11% hepatic
  - 8% endocrine
  - 52% of patients discontinued ipilimumab due to toxicity

Eggermont AM, et al. *Lancet Oncol.* 2015; 16:522-30.

Adjuvant Ipilimumab Approval

- FDA approved 10/28/2015
  - Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
- Dosing
  - 10 mg/kg IV over 90 minutes every 3 weeks x 4 doses followed by
  - 10 mg/kg every 12 weeks for up to 3 years until disease recurrence or toxicity

Yervoy (ipilimumab) prescribing information. Bristol-Myers Squibb. 2015 Oct.

Toxicity Comparison Between Ipilimumab and Interferon (IFN)

Grade 3 Toxicity	Interferon[i]	Ipilimumab[ii]
Any	40%	46%
Diarrhea	-	10%
Colitis	-	7%
Fatigue	15%	2%
Endocrinopathy	-	8%
Transaminitis	10%	4%
Myalgias	4%	-

i. Eggermont AM et al. *Lancet.* 2008; 372:117-26.
ii. Eggermont AM et al. *Lancet Oncol.* 2015; 16:522-30.

Management of INFα Adverse Effects

Symptom*	Evaluation	Management
Anorexia	Anorexia, weight loss, early satiety	Nutritional assessment, small frequent meals, high protein supplements
Fatigue	Patient performance	Hydration, assess coexisting illnesses, improve nutrition, schedule activity
Depression	Routine screening	Consider antidepressant, assess other causes (medications), test thyroid, psychiatric consultation
Flu-like symptoms	Fever, chills, headache, myalgia, nausea/vomiting	Hydration, analgesics, antiemetics, rule out infection (>39 ºC), bedtime administration

*For >grade 3 adverse effects, may hold therapy and reduce dose by 33%-50% at re-initiation

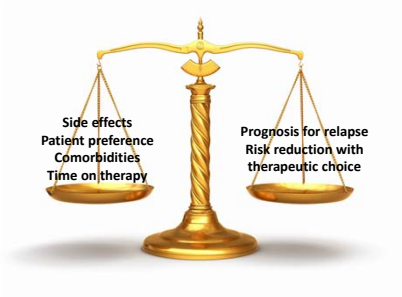
Hauschild A et al. *Cancer.* 2008; 112:982-94.

IFN Dosing Adjustments

- IFN dose limiting toxicities (DLT):
  - Granulocytopenia <500 cells/mm^3
  - Increased liver enzymes >5 times normal
- Withhold dose until DLT resolves to ≤grade 1
- Resume IFN at a reduced dose:
  - 33% dose reduction after 1st event
  - 66% dose reduction after 2nd event
  - Discontinue therapy after 3rd event

Kirkwood et al. *J Clin Oncol.* 2002; 20:3703-18.

Therapeutic Dilemma



Which adjuvant treatment option would you recommend for this Stage IIIc melanoma patient?

a. Ipilimumab 10 mg/kg
b. Ipilimumab 3 mg/kg
c. Interferon alfa-2B
d. No adjuvant therapy

Addressing Cost Concerns

How often does the cost of an immunotherapy drug factor into your clinical decision making?

a. Very frequently
b. Sometimes
c. Infrequently
d. Never

"Try to focus less on a cure and more on a treatment you can afford."

Drug Costs

- Eleven of the 12 cancer drugs approved by the FDA in 2012 cost >$100,000 per year
- The U.S. spent more on cancer drugs last year—$37 billion, up 19% in five years—than any other category
- Overall costs for treating cancer are well over $100 billion annually and mounting steadily

Wall Street Journal, May 27, 2014.

"Financial Toxicity"

- High cost-sharing = negative impacts on medication adherence and health outcomes
  - Kaiser Family Foundation study found 1 in 3 Americans have difficulty paying medical bills
- Cancer patients 2.65x more likely to file for bankruptcy than those without cancer
  - Only 21% of patients surveyed in a recent analysis actually chose to discuss their fears with a professional

Financial Toxicity Concerns

- Cost of drug acquisition
- Cost of toxicity management
- Cost of loss of work days, etc.

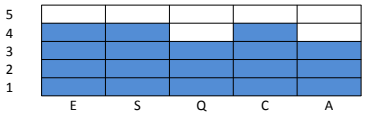
Benefits Come at a Cost

Parameter	Ipilimumab	Pembrolizumab	Nivolumab
Response rate	10.9%	33.7%	43.7%
Cost per dose	$30,694	$7,251	$6,043
Average number of doses	4	8	10
Estimated cost per patient	$122,776	$48,344	$44,956
Grade 3-5 toxicities	10-26%	9-36%	12-42%

Slide courtesy of Neil Mason, MBA, Personalized Medicine Strategist, Moffitt Cancer Center

Cost and Value Metrics

An example of NCCN Evidence Blocks
Categories and Definitions



E=efficacy of regimen/agent
S=safety of regimen/agent
Q=quality of evidence
C=consistency of evidence
A=affordability of regimen/agent

Each measure is scored from 1 to 5, with 1 least favorable and 5 most favorable

Provider Resources

- New online programs for providers to help find right programs for patients

Future Directions

- Institutional pathways to guide appropriate decision making
- Prescription drug benefit programs that may be able to negotiate price based on volume
- Unclear whether federal legislation will permit drug price negotiation
- Efforts by NCCN, ASCO to help establish drug value (i.e., outcome / investment)

Key Takeaways

- Key takeaway #1: TVEC is safe and effective for the treatment of cutaneous metastases in advanced melanoma
- Key takeaway #2: The use of interferon vs. ipilimumab in the adjuvant setting depends largely on patient selection and careful risk/benefit assessment
- Key takeaway #3: Patient assistance programs and emerging value metrics in immuno-oncology are essential to effective, affordable treatment strategies

Self-assessment Questions

The presentation self-assessment questions are listed here for your convenience. Note the correct answers for future reference.

1. Which of the following is FALSE regarding T-VEC?
   a. The dose administered is based on the size of the lesion(s) being injected.
   b. Doses may be prepared up to 24 hours prior to injection.
   c. Immunosuppressed contacts are at risk of HSV1 infection if they touch the patient's occlusive dressing.

2. Which adjuvant treatment option would you recommend for this Stage IIIc melanoma patient?
   a. Ipilimumab 10 mg/kg.
   b. Ipilimumab 3 mg/kg.
   c. Interferon alfa-2B.
   d. No adjuvant therapy.

3. How often does the cost of an immunotherapy drug factor into your clinical decision making?
   a. Very frequently.
   b. Sometimes.
   c. Infrequently.
   d. Never.