Bridging the Gap in Understanding Immuno-Oncologic Treatments – An Interactive Webcast!

Presented by:
Anthony J. Olszanski, RPh, MD
Fox Chase Cancer Center

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Fox Chase Cancer Center

This activity is supported by educational grants from Bristol-Myers Squibb and Merck Sharp & Dohme Corp.

Opening Remarks

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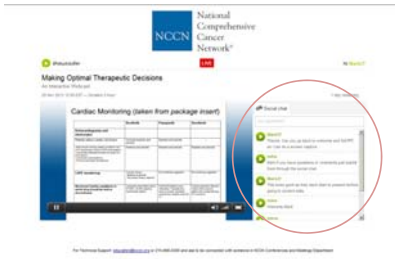

Opening Remarks

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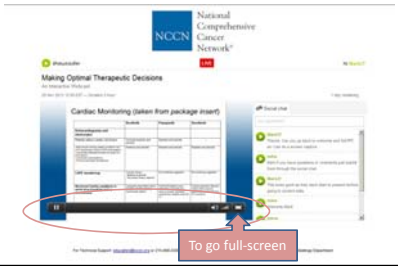

Accreditation Information

- Credit will be provided to physicians, nurses, and pharmacists (1.25 contact hours) through completion of an evaluation and post-test. All registered participants will receive an e-mail from our CE and Grants Department within 3-5 business days with instructions on how to access this evaluation and post-test at http://education.nccn.org/node/50904. Certificates will be generated automatically upon successful completion of this step. Should you not receive an e-mail within 5 days, please contact us at education@nccn.org.
- If you participated with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity. Lists can be sent to education@nccn.org and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.
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Accreditation Information

Intended Audience:

This webcast is designed to meet the educational needs of medical oncologists, community oncologists, oncology fellows, oncology nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

Learning Objectives:

Following this program, participants should be able to:

- Provide an overview of the role of the human immune system in cancer
- Outline the underlying principles of immunotherapy and mechanisms of action of immunotherapeutic agents for the treatment of cancer
- Summarize evidence of efficacy of immunotherapy in cancer, especially in melanoma
- Describe the unique response pattern and toxicity profile of immunotherapy and required surveillance and monitoring

Accreditation Information

Physicians

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NCCN designates this live activity for a maximum of 1.25 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.

Accreditation Information

Pharmacists

Pharmacy Educational Objective
After completing this activity, the participant should be able to:
•Provide accurate and appropriate counsel as part of the treatment team.

Accreditation Statement

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of Activity
Knowledge

Credit Designation
National Comprehensive Cancer Network designates this continuing education activity for 1.25 contact hour(s) (0.125 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

UAN: 0836-0000-14-084-L01-P

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Cancer Net.LLC: Honoraria
iCeutica: Scientific Advisor
Merck: Scientific Advisor
Millennium: Scientific Advisor
Santaris: Scientific Advisor

Matthew R. Zibelman, MD
None

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AstraZeneca Pharmaceuticals: Equity Interest/Stock Options

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Maria Ho, PhD

While NCCN is pleased to respond to as many questions as possible during this webcast, NCCN will not be able to respond to your individual questions of a clinical nature after the webcast has concluded. We are also not able to offer recommendations on patient care regarding specific cases.

Faculty Biographies

Anthony J. Olszanski, RPh, MD, is Associate Professor, Director of the Phase 1 Developmental Therapeutics Program, and Director of the Medical Oncology Melanoma Program at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Dr. Olszanski earned his medical degree from the University of Medicine and Dentistry of New Jersey. He completed internal medicine training, hematology/oncology and clinical pharmacology fellowships at Dartmouth-Hitchcock Medical Center. Dr. Olszanski is board certified in Internal Medicine, Medical Oncology, and Clinical Pharmacology.

Dr. Olszanski's primary research interests lie in phase 1/early drug development of biologics/targeted agents and the pharmacodynamics of single transduction pathway perturbation. He specializes in the oncologic care of gastrointestinal malignancies and melanoma.

In addition to his role on multiple committees at Fox Chase Cancer Center, Dr. Olszanski also sits on the American Board of Clinical Pharmacology and the NCCN Melanoma Panel. He is author or co-author of various peer-reviewed publications and abstracts.

Matthew R. Zibelman, MD, is a Hematology Oncology Fellow at Temple Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Dr. Zibelman earned his medical degree from Temple University School of Medicine. He completed his residency in internal medicine at the University of Illinois at Chicago Medical Center. While there, Dr. Zibelman served as Chief Resident of Internal Medicine. He was also Assistant Professor of Medicine at the Medical College of Wisconsin in Milwaukee, WI.

Dr. Zibelman's research interests include melanoma, renal cell carcinoma (RCC), and prostate cancer. His primary research interest is the role of immunotherapy in the treatment of malignancies, specifically checkpoint inhibitors in melanoma and RCC.

Dr. Zibelman has received numerous awards and honors, is a member of several professional societies, and has authored many publications including book chapters, abstracts, posters, and editorials. He is an invited lecturer and active in community service.

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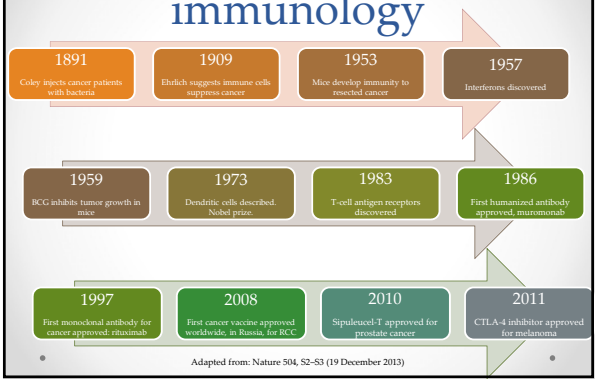
Timeline of cancer immunology

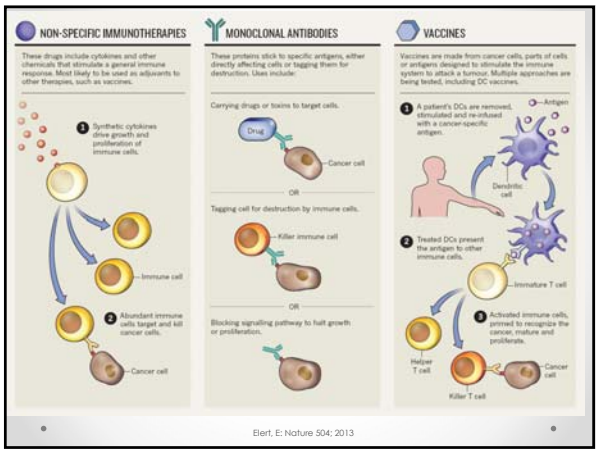


Adapted from: Nature 504, S2–S3 (19 December 2013)

Immunotherapy

- 1891, William Coley injected cancer patients with bacteria to ignite an immune response
- Agents under investigation currently – partial list:
  - PD-1 and PD-L1
  - Interleukins 7, 15, 21
  - Anti-CD25
  - IDO inhibitors
  - TLR agonists
  - TIL and ACT

http://www.nature.com/ni/journal/v14/n10/full/ni.2703.html
http://www.nature.com/nature/journal/v504/n7480_supp/full/504S1a.html
http://www.nature.com/nature/journal/v504/n7480_supp/full/504S13a.html



Elert, E: Nature 504; 2013

Immunoediting hypothesis

Elimination phase	• active immune surveillance may eradicate tumor
Equilibrium phase	• balance between eradication of some susceptible cells and non-eradicated tumors developing mechanisms to evade detection
Escape phase	• tumor growth due to reduced immunogenicity or enhanced immunosuppressive mechanisms

Adaptive mechanisms of escape

- Expression of immune-inhibitory molecules
  - Examples: CTLA-4 and PD-1
- Presence of immunosuppressive regulatory T lymphocytes (Tregs)
- Increased immunosuppressive cytokines within the tumour microenvironment
- Down-regulation of major histocompatibility molecules
- Down-regulation of tumour antigens leading to reduced antigen presentation and recognition

Immunoregulatory molecules & prognosis

- PD-L1 expression is widely expressed
- Expression of PD-L1 is associated with reduced survival and poor prognosis in:
  - Lung
  - Renal
  - Pancreatic
  - Ovarian

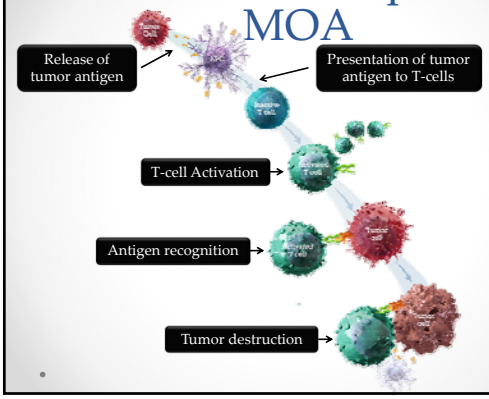
Tumor-infiltrating lymphocytes (TILs)

- Cytotoxic T-cells correlate with improved prognosis in:
  - Colorectal
  - Melanoma
  - Lung cancer
  - GIST
  - Ovarian
  - Breast
  - Renal

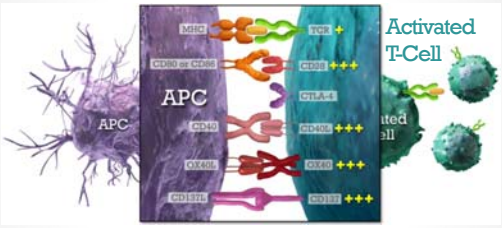
Differentiation of CTLA-4 and PD-1

- Expression
  - CTLA-4 is restricted to hematopoietic system
  - PD-L1 also expressed on a wide variety of tumors
- T-cell control (early vs late) may lead to differing AE profile
  - CTLA-4 controls early T-cell activation
  - PD-L1 acts later in T-cell response

Anti-tumor response MOA

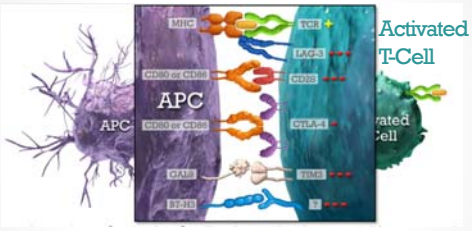


T-cell Activation



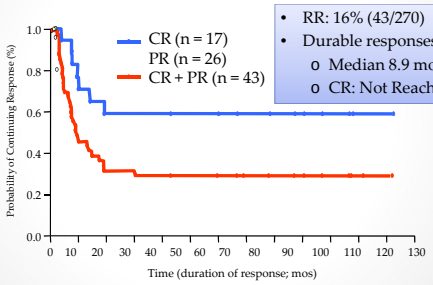
Multiple activation pathways through:
- CD28
- CD40
- OX40
- CD137

T-cell Inhibition



Multiple negative regulators:
- LAG-3
- CTLA-4
- B7-H3

High-Dose IL-2 Therapy



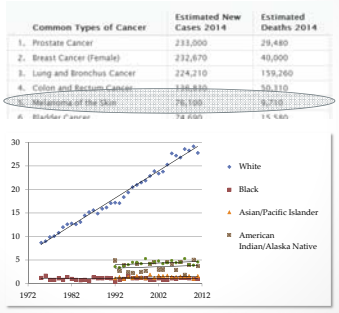
- RR: 16% (43/270)
- Durable responses
  - Median 8.9 mos
  - CR: Not Reached

Atkins et al, 1999.

Melanoma 2014

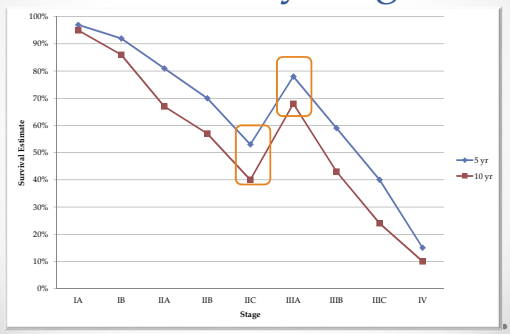
- Most common form of cancer age 25-29
- Accounts for <5% of skin cancers but >75% of skin cancer deaths
- Median age at diagnosis: 62 yrs
- Early metastatic potential
- Early and common CNS seeding
- Historic lack of effective systemic therapies (until recently)
- Among leading tumors in years of life lost

Rising Incidence



SEER Stat Fact Sheets: Melanoma of the Skin. http://seer.cancer.gov. Accessed 5/22/2014

Survival by Stage

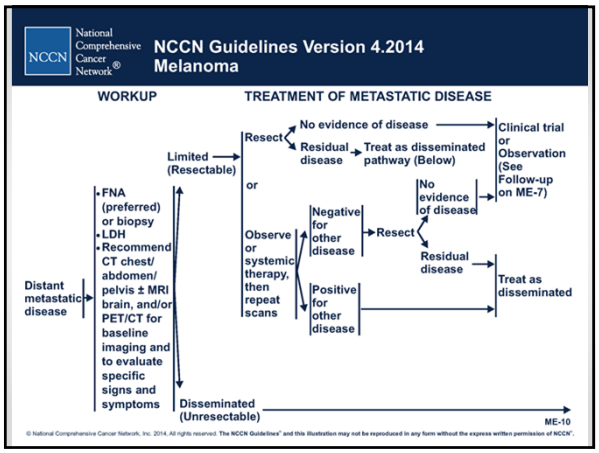


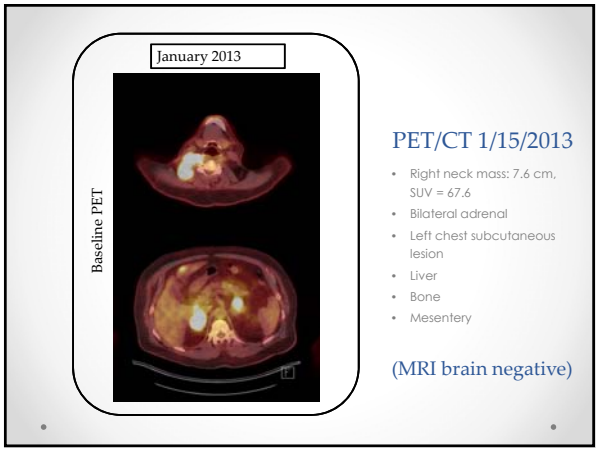
Patient

- 45 year old male
- PMHx: Prostate CA, s/p XRT; HTN; A. Fib
- SocHx: Married, two children in their 20's
- Remote 14 pk yr smoking hx, 6 EtOH drinks/week
- No family hx melanoma or pancreatic cancer
- Prior history of excessive sun exposure confirmed

HPI

- Summer of 2012 patient noticed small left neck "lump"
- Biopsied August 2012
  - Pathology: melanoma, S100, HMB-45, MART-1 positive
- Patient lost to follow-up until January 2013
- ROS: PS=0, mild fatigue only
- Exam: 6-7 cm large firm, fixed, left neck mass appreciated with hyperpigmented central area. At least 2 firm palpable lymph nodes just inferiorly, slightly mobile
- Primary site NOT identified
- LDH = 758 (313-618)

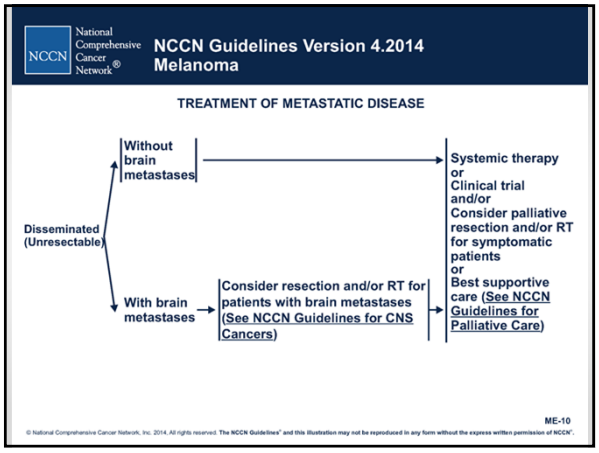




PET/CT 1/15/2013

- Right neck mass: 7.6 cm, SUV = 67.6
- Bilateral adrenal
- Left chest subcutaneous lesion
- Liver
- Bone
- Mesentery

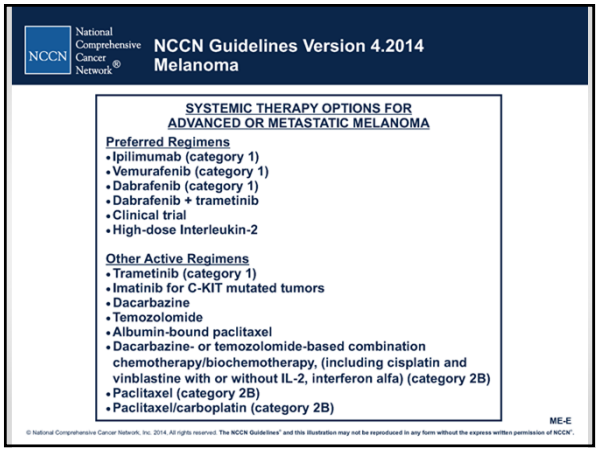
(MRI brain negative)



Molecular testing

- "Obtain tissue for genetic analysis from either archival material or biopsy of the metastasis if the patient is being considered for targeted therapy or if the tissue is relevant to eligibility for participation in a clinical trial"

  (NCCN Guidelines Version 4.2014)
- BRAF, c-KIT, NRAS testing

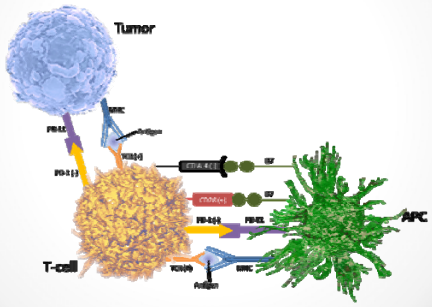


Treatment course

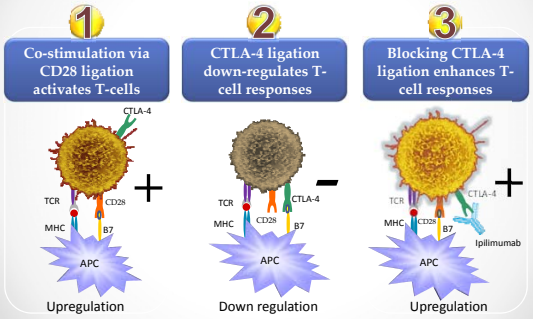
- Clinical trial offered, but not eligible due to prior hx of prostate cancer
- Molecular tests for BRAF and c-KIT pending
- Ipilimumab 3 mg/kg initiated 1/25/2013
  - TSH normal

symptoms. Patients with low-volume, asymptomatic metastatic melanoma may be good candidates for immunotherapy (ipilimumab or IL-2), as there may be time for a durable antitumor immune response to emerge. Patients with BRAF-mutant melanoma who have symptomatic disease or who have progressed despite immunotherapy should be considered for targeted therapies. Clinical trials are underway to address unanswered questions regarding the optimal sequencing

Immune Checkpoints



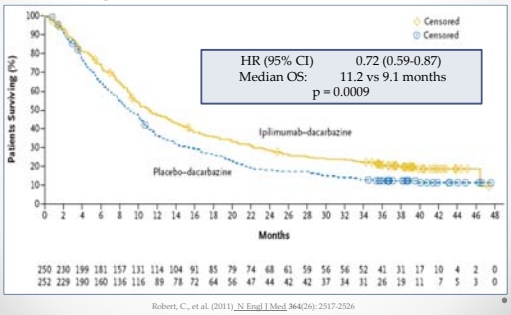
Anti-CTLA-4 Mechanism of Action



Fong et al, 2008

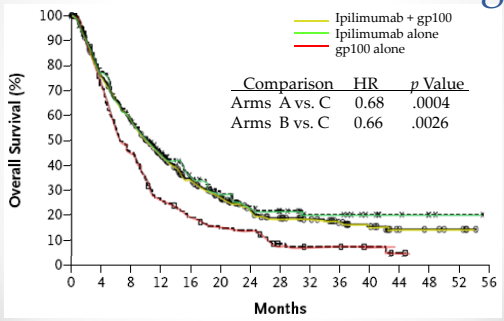
Survival in 1st line setting

Ipilimumab Plus Dacarbazine Vs. Dacarbazine: OS



Robert, C., et al. (2011) N Engl J Med 364(26): 2517-2526

Survival in 2nd line setting



Hodi FS, O'Day SJ, McDermott DF, et al: N Engl J Med 363:711-23, 2010

H&P preceding dose #2

History
- Primary lesion on the left side of his neck is "bruised, raised and blistered looking"
- Began 2 weeks after 1st dose of ipilimumab
- No pain but patient states: "ugly to look at"

Physical
- Significant size lesion, > 7cm, on the left side of his neck
- Extending medially from under his ear into his supraclavicular area
- New raised, approximately 1.5 cm x 4 cm darkened area in the middle of this lesion (not present on prior exams)
- The skin covering this particular portion of his larger lesion is very thin and approaching breakdown as it appears as though his tumor is starting to necrose the skin

Plan
- Proceed with dose #2; Refer patient to radiation oncology

Concurrent XRT and CTLA4 inhibition

- 166 patients treated with RT and ipilimumab
  - 117 non-brain
  - 81 brain
- Radiotherapy given during induction phase and maintenance phase
- AE rates with concurrent XRT were not higher than expected
- Potential for abscopal effect: tumor regression at a site distant from the primary site of radiotherapy

Barker CA et al. Cancer Immunol Res 2013;1:92-98
Postow MA et al. NEJM 2012;366:925-31

H&P preceding dose #3

History
- Patient presents for evaluation prior to receiving dose #3 of ipilimumab
- Has completed XRT to left neck: 20 Gy in 5 fractions. Feels he tolerated well except for some minor oral ulcers
- Also mentions a secondary complaint of intermittent blurry vision which he attributes to needing new glasses

Physical
- unremarkable ocular exam
- Oral ulcerations appreciated (R>>L)
- Left neck mass now measuring 10 cm and is hard and firm

Plan
- Proceed with dose #3 of ipilimumab under condition patient is evaluated by ophthalmologist
- Therapeutic mouthwash and oral care prescribed for ulcers

Toxicity evaluation 8 days later

History
- Patient presents for evaluation reporting worsening oral pain and ulceration
- Has not yet seen ophthalmology, denies changes in vision

Physical Exam
- Worsening oral ulceration and visible thrush
- Mild conjunctival irritation noted

Plan
- Started on nystatin for candidiasis
- Encouraged to see ophthalmology

5 days later

History
- Patient presents to clinic for evaluation complaining of worsening fatigue and progressive vision changes
- Can only see shapes. However "everything is fine" he states, as he saw ophthalmology who feels he has melanoma-associated retinopathy syndrome (MARS), but was not placed on any treatment

Physical Exam
- Significant conjunctival inflammation noted

Plan
- Patient admitted for treatment with high-dose steroids

CTLA4: Select AEs

	Ipilimumab + Dacarbazine (n = 247)		Placebo + Dacarbazine (n = 251)	
	Total	Grade 3/4	Total	Grade 3/4
Dermatologic				
Pruritus	29.6	2.0	8.8	0
Rash	24.7	1.2	6.8	0
GI				
Diarrhea	36.4	4.0	24.7	0
Colitis	4.5	2.0	0.4	0
GI Perforation	0	0	0	0

❖ Select AEs are shown, regardless of attribution

Wolchok et al, 2011

CTLA4: Select AEs (cont.)

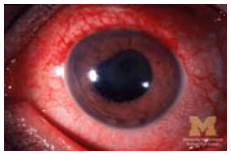
	Ipilimumab + Dacarbazine (n = 247)		Placebo + Dacarbazine (n = 251)	
	Total	Grade 3/4	Total	Grade 3/4
Hepatic				
Increased ALT	33.2	21.9	5.6	0.8
Increased AST	29.1	18.2	5.6	1.2
Endocrine				
Hypothyroidism	1.6	0	0.4	0
Thyroiditis	0.8	0	0	0
Hyperthyroidism	0.4	0	0.4	0
Hypophysitis	0	0	0	0

❖ Select AEs are shown, regardless of attribution

Wolchok et al, 2011

Visual disturbance with ipilimumab

- Uveitis/iridocyclitis < 1% of patients
- Autoimmune reaction
- Eye redness, irritation, blurred vision, pain, photophobia



Jonathan Trobe, M.D., University of Michigan Kellogg Eye Center

Uveitis treatment

- Ophthalmology referral
- Topical steroids for grade 1-2 (ophthalmology prescribed)
- Systemic steroids for grade 3-4, with slow taper

In-patient hospital course

- Labs on admission reveal patient has acute kidney injury as well, presumed autoimmune
- Started immediately on high dose steroids with IV methylprednisolone
- Within 2 days, renal fxn improving, but vision still blurry. Fatigue gone
- Renal biopsy considered but not done as creatinine back to baseline
- Continued improvement through hospital day #5, discharged with normal renal function and near normal vision

Post-hospital admission follow-up

History
- Vision continuing to improve, energy back to baseline
- New complaint of pruritic, erythematous rash on scalp with associated hair loss

Physical Exam
- No conjunctival inflammation or oral ulcers
- Pustular, folliculitis-like rash of entire scalp noted with areas of alopecia
- Neck lesion has nearly become flat
- Right axillary node and previously noted right chest wall lesion both no longer palpable

Plan
- Ipilimumab permanently discontinued, despite patient objections
- Started on topical mupirocin ointment to scalp and referred to dermatology
- Re-staging PET scan planned before next visit

Dermatologic immune-related Aes (irAEs)

- Common irAEs
  - Mostly low grade
  - Rash, pruritus, vitiligo
  - Resolves with symptomatic therapy or corticosteroids
  - Frequently associated with T-cell infiltrate

Hodi et al, 2003; Beck et al, 2006; Attia et al, 2005.

Potentially fatal irAEs

- 7% enterocolitis
  - ≥ 7 stools/day over baseline; peritoneal signs of bowel perforation; ileus; fever; need for IV hydration > 24 hrs; GI hemorrhage
- 4% hypopituitarism/adrenal insufficiency
  - Fatigue; headache; MS changes; abdominal pain; hypotension; TFT abnormalities
- 3% dermatitis
  - Steven-Johnson Syndrome; Toxic epidermal necrolysis; Full thickness rash with dermal ulceration; necrotic, bullous or hemorrhagic manifestations
- 2% hepatitis
  - AST/ALT > 5 X ULN; T BILI > 3 X ULN
- 1% neuropathy
  - Impact on ALDS with: Weakness, sensory alteration or paresthesia
- 1% nephritis
- 1% eosinophilia

Others:
- Pneumonitis
- Meningitis
- Pericarditis

Gastrointestinal irAEs

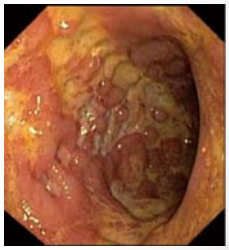
- Diarrhea is a frequent irAE
  - Most cases are mild or moderate
  - Biopsy demonstrates inflammatory colitis, T-cell infiltrates
  - Most cases respond to either symptomatic treatment or steroids
  - GI perforation (< 1%) requiring surgery

Autoimmune colitis

- Diarrhea, abdominal pain, peritoneal signs, ileus, fever
- Up to 31% of patients overall (Diarrhea + colitis)
- True autoimmune colitis occurs in up to 5% of patients, with 2% ≥ G3
- Rule out infectious etiologies
- Grade 1-2: < 6 BM/day; < 24 hours
  - Loperamide, Lomotil, oral steroid
- Grade 3-4: > 7 BM above baseline; > 24 hours
  - Permanently discontinue ipilimumab
  - Consider colonoscopy
  - Steroids 1-2 mg/kg/day
  - Taper over 4 weeks when resolved
  - For inadequate response: infliximab

Autoimmune colitis treatment

- Grade 1-2 often can be treated symptomatically
  - Low-motility agents
  - Oral budesonide
- Grade ≥ 3 requires systemic steroids
  - Can be associated with bowel perforation
  - Colonoscopy can be considered for diagnostic confirmation
- If persists (eg, 1 wk), consider infliximab 5 mg/kg IV (TNF-blocking antibody)



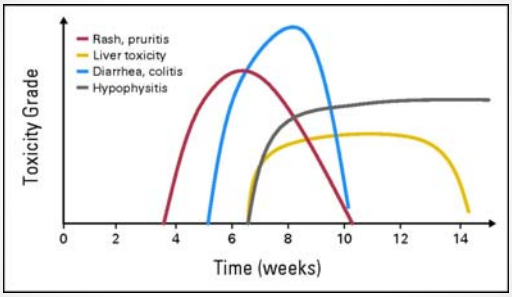
Endocrinopathy irAEs: Overview

- Symptoms: Fatigue, nausea, amenorrhea, impotence, hypotension, hyponatremia, hypoglycemia, eosinophilia
  - If strong suspicion for adrenal crisis (dehydration, hypotension) start stress dose steroids
- Endocrine labs: ACTH, cortisol, TSH
  - Closely follow; if grade 2 toxicity, continue ipilimumab
  - Hormone replacement; consider trial of high-dose steroids if needed
  - If suspect hypophysitis, head MRI with pituitary cuts; visual field testing

irAE Management: Summary

- Patient education for early recognition of irAEs
- Aggressive work-up and management for moderate/severe events
- Non-specific complaints
  - o May reflect endocrine (e.g., pituitary) toxicity
- Established therapies (e.g., corticosteroids) are effective
- Algorithms established for work-up, treatment, and reporting of irAEs
- Appropriate patient education upon discharge

Kinetics of adverse events



Weber J S et al. JCO 2012;30:2691-2697

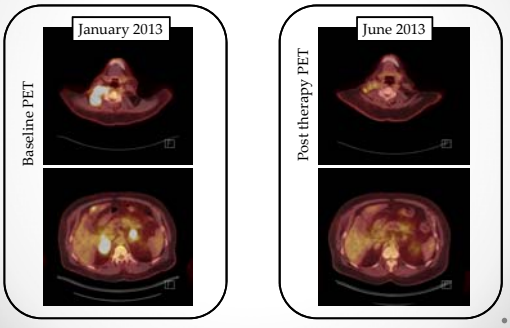
Follow-up visit with re-staging PET scan

History

- Hair now growing back, but white, pruritus improved
- No new palpable lesions
- Vision and energy level back to normal
- Sig improvement in performance status and exam unremarkable

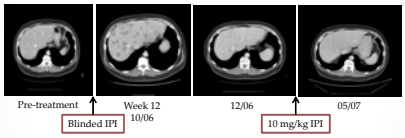
- PET/CT scan reveals very good partial response

Response to ipilimumab treatment



Pseudo-progression, delayed response, and benefit

- Not all patients respond at time of first scan
  - Some patients appear to have more disease (pseudo-progression)
  - Some patients have a response occurring after the 1st disease assessment

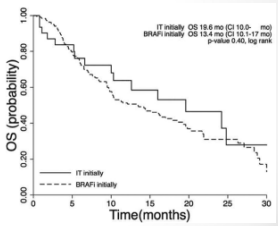


- Not all patients respond but may have clinical benefit

Prieto P et al. CCR 2012
Wolchok J et al. CCR 2009
Images courtesy of Dr. Wolchok
Yvonne M. Saenger and Jedd D. Wolchok; Cancer Immunity, Vol. 8, p. 1 (17 January 2008).

Sequencing Ipi pre/post BRAF

- IT→BRAF OS 19.6 m vs BRAF→IT OS 13.4 m (p 0.4)
- No difference in OS or PFS based on sequencing
- ORR of BRAFi therapy is similar in patients who did or did not receive prior IT
- mOS post BRAFi discontinuation is short
- Ipilimumab therapy following BRAF inhibitors was associated with no tumor responses and poor survival



Ackerman, et al. Cancer 2014

Discussion points

- Selection of 1st line therapy
  - Immunotherapy in BRAF WT tumors
  - Stratification of BRAF + tumors
    - Low volume
    - Asymptomatic
    - Symptomatic disease
    - Progression post immunotherapy

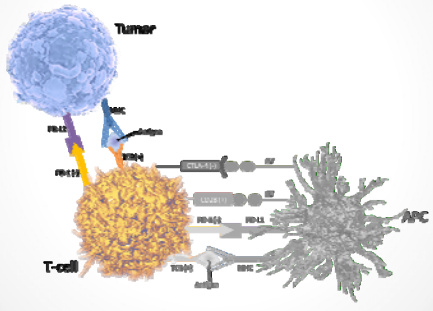
Consider Immunotherapy

Targeted Agents

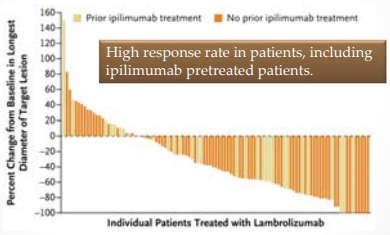
The (near) future of immunotherapy

Anti-PD-1 and PD-L1 inhibitors

Anti-PD-1 MOA

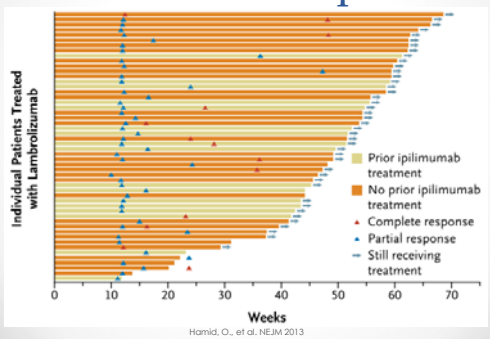


Pembrolizumab anti-PD-1



Hamid, O., et al. NEJM 2013

Anti-PD-1 onset and duration of response



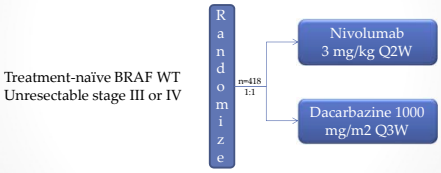
Hamid, O., et al. NEJM 2013

Nivolumab associated AEs

	Any Grade n (%)	Grade 3-4 n (%)
Any	58 (54)	5 (5)
Skin	38 (36)	2 (2)
Gastrointestinal	19 (18)	2 (2)
Endocrinopathies	14 (13)	2 (2)
Hepatic	7 (7)	1 (1)
Infusion Reaction	6 (6)	0
Pulmonary	4 (4)	0
Renal	2 (2)	1 (1)

High-level PD-1 results

- June 25, 2014 press release
- 1st line trial reports OS benefit in nivolumab trial



Summary

- Current immunotherapy approaches (IL-2; CTLA-4) lead to a response in the minority of patients but may lead to extremely durable disease control
- Adverse event management of CTLA-4 inhibitors is successful with patient and health-care team education → early recognition and treatment
- Emerging evidence suggests that most BRAF mutation positive patients should be treated with immunotherapy first – may impact survival
- Newer approaches using PD-1 and PD-L1 antibodies appear to lead to responses in a much higher proportion of patients and are durable

Current Recommendations

- Clinical trials using immunotherapeutic approaches should be considered whenever possible
- Patients progressing after ipilimumab should be strongly considered for the pembrolizumab anti-PD-1 expanded access program now available at select sites

Please Remember!

- If you participated with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity. Lists can be sent to **education@nccn.org** and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.
- If you have not individually registered, please register at: **http://www.cvent.com/d/94q4qr**
- An e-mail will be sent within 3-5 business days with instructions on how to login to complete post-test and evaluation. These must be completed in order to receive a CE certificate. Contact **education@nccn.org** should you not receive this e-mail within 5 business days.
- For notification on upcoming educational events, join our group on LinkedIn: NCCN Conferences and Meetings Group or follow us on Twitter: @NCCNMeetings.