UNC N.C. CANCER HOSPITAL LINEBERGER COMPREHENSIVE CANCER CENTER

An Overview of Melanoma, 2017

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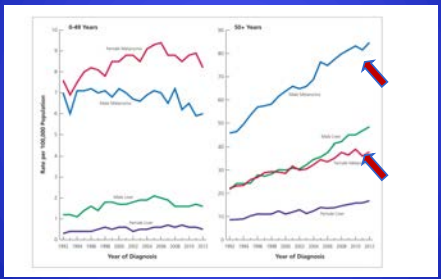
Educational Objectives

- Recognize melanoma skin cancer.
- Know the standard of care for each stage of disease including the new treatments for stage III disease
- Know how to recognize and manage the side effects of therapy
- For seasoned melanoma practitioners, know what is new.

What is new

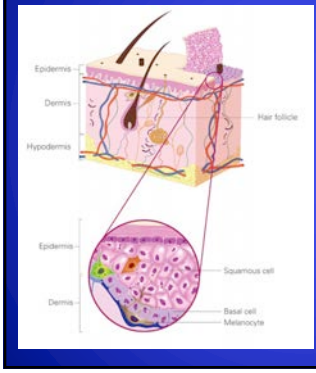
- Staging
- Nodal surgery
- Stage III adjuvant therapy
- Stage IV paradigms
- Treatment of brain mets.

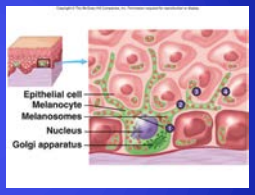
Incidence trends for melanoma and liver cancer by age, US.



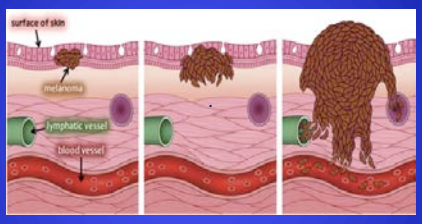
CA: A Cancer Journal for Clinicians
Volume 66, Issue 1, pages 7-30, 7 JAN 2016 DOI: 10.3322/caac.21332
http://onlinelibrary.wiley.com/doi/10.3322/caac.21332/full#caac21332-fig-0003

Normal Skin-Cell Components





How Does Melanoma Progress?

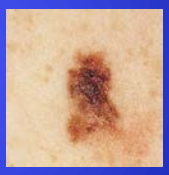


Breslow Ann Surg 1970

- Thickness
- Ulceration
- Mitoses

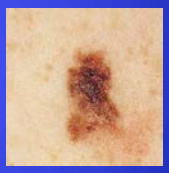
Case 1

- A 49 year old married father of two presents on the urging of his wife due to a mole on his right lower leg that seems to have changed. He is in good health and takes no medication. The mole is shown. The rest of the examination is normal.



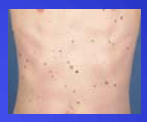
Additional history

A—Asymmetry
B—Border
C—Color
D—Diameter
***E—Evolution: A changing mole**



Phenotypic Risk Factors

Increased nevi



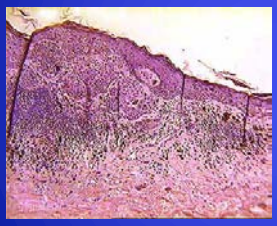
Fair skin
Red hair
Blue Eyes
↑Burnability
↓Tannability

Family history

Wickelgren, I. Science 2007;315:1215

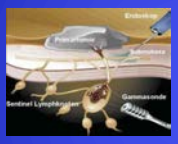
-Multiple melanomas, pancreatic cancer,(CDKN2A, p16).

Back to Case 1

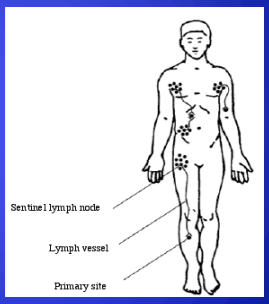


- Histologic type: Superficial spreading melanoma
  Breslow depth: 1.8 mm
  Ulceration: PRESENT

Sentinel Lymph Node Procedure/Clear the margins



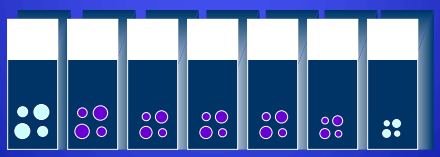
Morton N Engl J Med 355 2008



Sentinel Lymph Node Evaluation

Lymph node serially sectioned while fresh

Alternate sections paraffin-embedded; remainder snap frozen



Five H&E-stained sections flanked by two S-100 sections

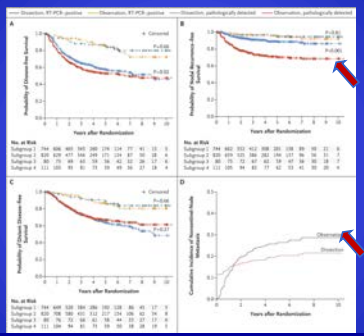
Case 1

- The sentinel lymph node procedure maps to the right groin. There are two sentinels nodes there. They are sent to pathology and sectioned. Two of the nodes contains melanoma cells. One has at least 1mm of cells.

MSTL II: Completion Dissection or Observation in Sentinel-Node + Melanoma

- 1939 patients randomized
- The observation group were monitored every 4months for the first 2 years and every 6 months for years 3 through 5. Ultrasound of the nodal basin occurred at each visit.
- Follow up of the dissection group followed the same schedule but the ultrasound was not done.

Disease-free Survival, Survival without Nodal Recurrence, and Distant Metastasis–free Survival, According to Trial Group, and the Cumulative Rate of Nonsentinel-Node Metastasis.



Immediate completion lymph-node dissection reduced the rate of regional nodal recurrence by nearly 70%. Overall survival is unchanged. Completion dissection completes staging.

The surgeon recommends a : Completion Nodal Dissection

- Diagnosis:
  Lymph node dissection, Right inquinal nodes
  - Thirteen negative lymph nodes (0/13).
- -Total nodes 2/15

AJCC Staging 1/2018

T

T0: No evidence of primary tumor
Breslow depth
Ulceration
(Mitoses are no longer part of the staging.
T1 category uses 0.8mm as a threshold with T1b of 0.8-1mm w or w/o ulceration

N

N0
N1 one node is involved
N2 two to three
"c" categories for microsatellites and in-transit metastases

M

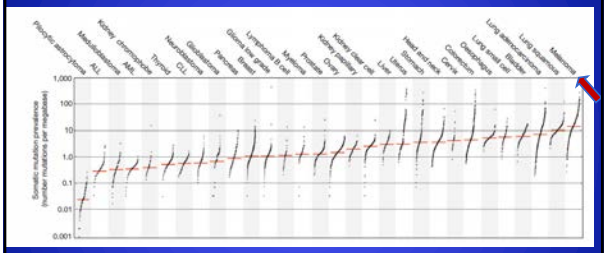
M1a-skin, subcutaneous tissue or distant lymph nodes
M1b-lung
M1c-other site
M1d-CNS

Stage I, II negative nodes
Stage III, positive nodes

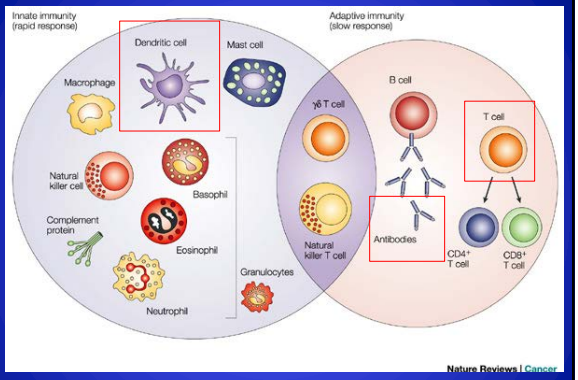
T2bN2aM0 Stage IIIb

Lets take a few minutes to go over some basic biologic principles

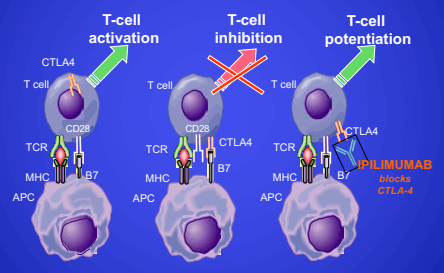
Neoantigen Prediction



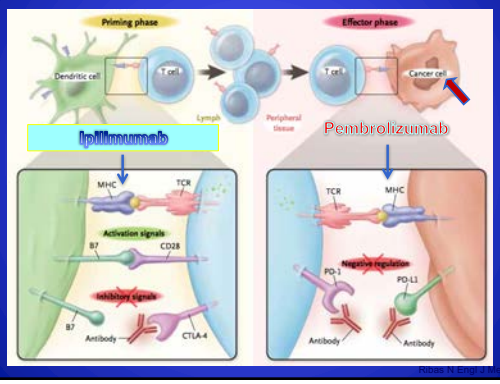
22 AUGUST 2013 | VOL 500 | NATURE | 415



CTLA 4 Ipilimumab---Acts peripherally



Differences



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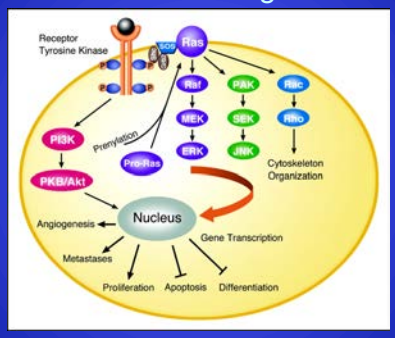
Ribas N Engl J Med 2012

Signal Transduction Pathways in Melanoma Oncogenesis



Beeram, M. et al. J Clin Oncol; 23:6771-6790 2005

JOURNAL OF CLINICAL ONCOLOGY

Double block

RAS

↓ ← BRAF inhibitor

RAF

↓ ← MEK inhibitor

MEK

↓

ERK

The patient has stage III melanoma.
Here are his choices:

1. Observation
2. Interferon
3. Nivolumab
4. ~~High dose ipilimumab~~
5. ~~Target therapy~~

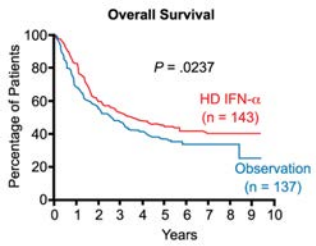
Observation

CLINICAL/ PATHOLOGIC STAGE	FOLLOW-UP	RE
Stage IIB - IV NED →	• See Common Follow-up Recommendations for All Patients[ll] • H&P (with emphasis on nodes and skin) ‣ every 3–6 mo for 2 y, then ‣ every 3–12 mo for 3 y, then ‣ annually as clinically indicated • Imaging[ll] as indicated to investigate specific signs or symptoms • Consider imaging[ll] every 3–12 mo[mm] (unless otherwise mandated by clinical trial participation) to screen for recurrence or metastatic disease (category 2B) • Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended after 3–5 years	

NCCN.org

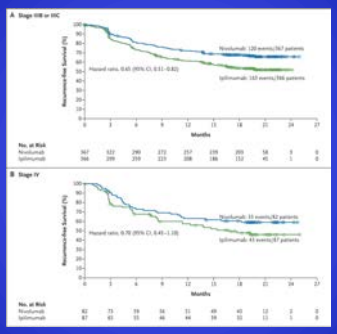
Adjuvant Interferon Alfa: ECOG 1684 Trial

- RFS and OS significantly improved with high-dose interferon α (HDI)
- Led to FDA approval of high-dose interferon α for adjuvant treatment of high-risk melanoma



PeerView press

CheckMate 238: Nivolumab or high dose ipilimumab Recurrence-free Survival, According to Disease Stage.



After 18 months 66.4% of patients who had nivolumab were free of disease compared to 52.7 percent of patients who got ipilimumab.

Weber J et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1709030

NEW ENGLAND JOURNAL of MEDICINE

Case 1

The patient choses Nivolumab and the authorization is sent to the insurance company.

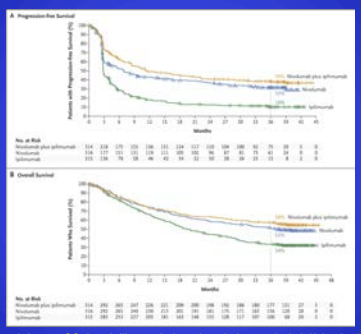
Case 2

A 55 year old who was treated for stage III melanoma three years ago presents for routine follow up. He points out a lump under the skin of his right upper arm that has been growing for three weeks. A CT/PET shows uptake in multiple nodules in the lung. A brain MRI and serum laboratory tests are normal. A lung biopsy is done and it shows recurrent melanoma. An IHC stain is + for the BRAF V600 E mutation.

Stage IV

- Median survival is improving---33 months
- 30% of patients with stage 4 melanoma may be cured.
- Surgery
- Radiation
  - Palliation of symptomatic sites
  - Brain Mets

CheckMate 067 Kaplan–Meier Estimates of Survival.

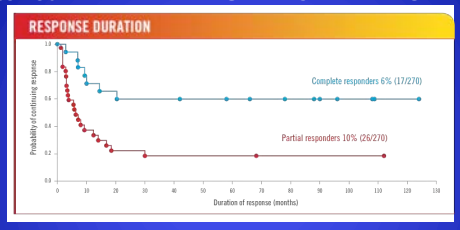


Ipi/nivo and Nivolumab longer OS than Ipilimumab. In a descriptive analysis ipi/nivo had better OS than nivolumab. 59% grade 3 or 4 toxicity in Ipi/nivo versus 21% in nivolumab alone.

Wolchok JD et al. N Engl J Med 2017;377:1345-1356.

The NEW ENGLAND JOURNAL of MEDICINE

Interleukin 2 IN METASTATIC MELANOMA



- In the metastatic melanoma studies:
  - Objective response was seen in 43 (16%) patients
  - 17 (6%) complete
  - 26 (10%) partial responders

Atkins et al. Cancer J Sci Am. 2000;6(suppl 1):S11-S14.

Choice of therapy

Immune therapy

- Generally preferred
- Combination versus single?
- Combination versus sequence?
- New Immune agents
- Biomarkers
- Caution with existing Autoimmune disease!

Target Therapy

- Hit the Target: BRAF V600E, 600K
- Generally works faster than immune therapy
- Difficult to stop

Case 2

The patient and his physician select pembrolizumab for his treatment.

Slide Effects of PD1 (and PDL 1 antibodies)

Other in less than 1%: dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures, adrenal insufficiency.

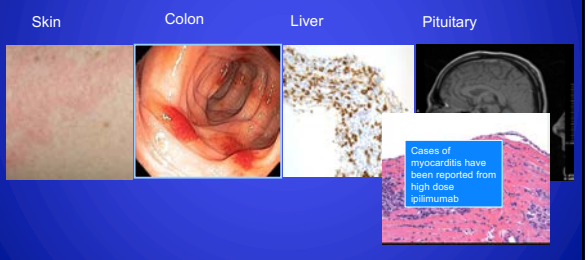
Case 2

Three months into treatment the patient is feeling well and he has not had any side effects from the therapy but a follow up cross sectional imaging study shows new tumors in the liver and right psoas muscle as well as mild increase in the baseline disease. His therapy is changed to ipilimumab.

Sequence of therapy

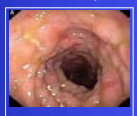
- A retrospective study of patients who had disease progression after treatment with PD1 inhibitors
- 47 patients were treated with ipilimumab and 37 were treated with ipilimumab and nivolumab. RR for ipi was 16% and the combination 21%. One year OS was 54% for ipi and 55% for ipi/nivo.
- Zimmer European Journal of Cancer 75(2017) 47-55

Side effects of Ipilimumab

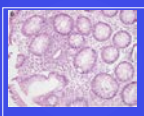


Diarrhea/Colitis

Immune-related colitis in a patient with metastatic melanoma treated with ipilimumab



Colonoscopic view of bowel edema and ulceration in the descending colon



Histopathologic analyses show focal active colitis (left) with crypt destruction, loss of goblet cells, and neutrophilic infiltrates in the crypt epithelium (right)

Maker AV, et al. Ann Surg Oncol 2005;12:1005-16

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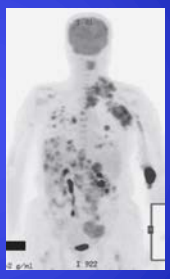
Case 2

Three months after ipilimumab started the patient returns for his check up. He has been having increase fatigue and pain in the right neck. Serum LDH is three times upper limit of normal. ECOG PS is 2.



Case 2

The patient's oncologist discusses the BRAF/MEK inhibitors with him and his wife and they choose this treatment.

-Dabrafenib/Trametinib
-Vemurafenib/Cobimetinib

BRAF/MEK I's

Dabrafenib/Trametinib

- Fever
  - Tylenol
  - Prednisone
- Arthralgia
- Trametinib is kept cold
- Empty Stomach.

Vemurafenib/Cobimetinib

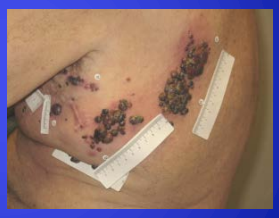
- Dermatologic
- Cardiac
- Rhabdomyelitis
- Does not need refrigeration
- No Food interaction

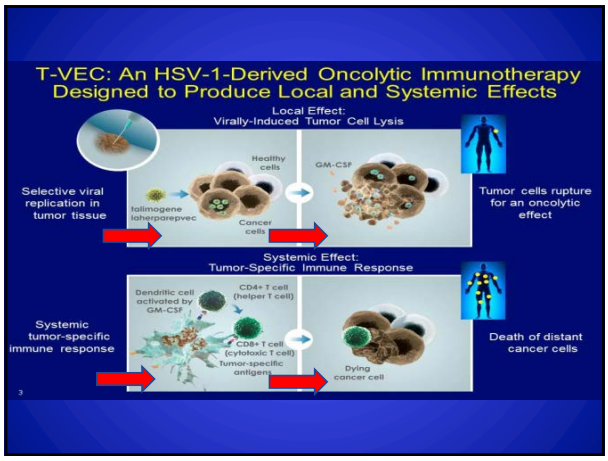
Be wary

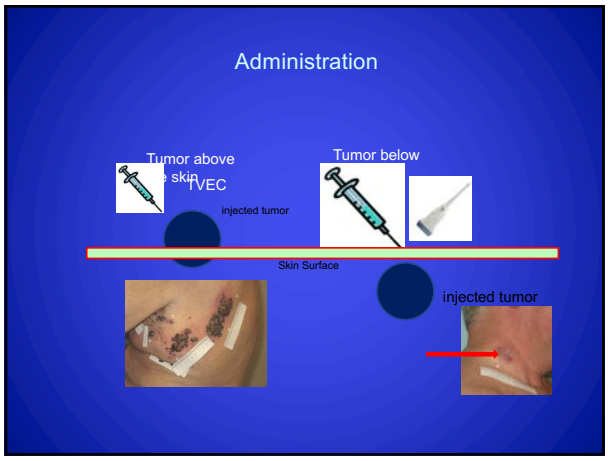
- Of the sequence of immune therapy and target therapy. Cases of Steven's Johnson have been reported.

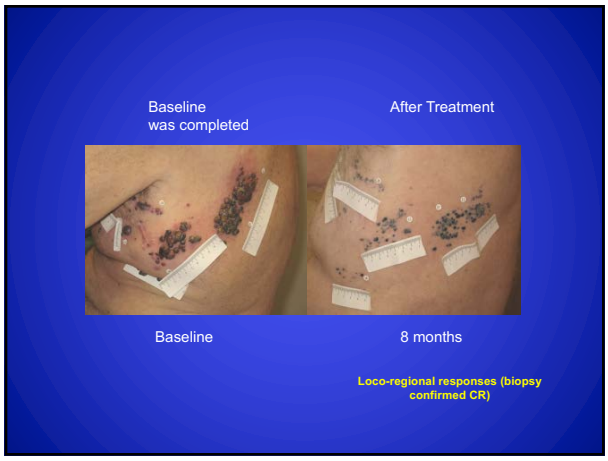
Case 3

- A 72 year old with myasthenia gravis is diagnosed with in transit melanoma. In three weeks the disease spread across his back and side body.




T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects
Local Effect:
Virally-Induced Tumor Cell Lysis
Selective viral replication in tumor tissue
talimogene laherparepvec
Healthy cells
GM-CSF
Cancer cells
Tumor cells rupture for an oncolytic effect
Systemic Effect:
Tumor-Specific Immune Response
Dendritic cell activated by GM-CSF
CD4+ T cell (helper T cell)
CD8+ T cell (cytotoxic T cell)
Tumor-specific antigens
Dying cancer cell
Systemic tumor-specific immune response
Death of distant cancer cells


Administration
Tumor above
skin
TVEC
injected tumor
Tumor below
Skin Surface
injected tumor

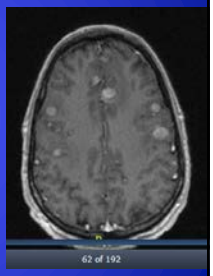

Baseline
was completed
After Treatment
Baseline
8 months
Loco-regional responses (biopsy confirmed CR)

Case 4

A 31 year old engineer was treated with interferon in the adjuvant setting. Three months into therapy a routine Chest CT showed three new pulmonary nodules in the LLL. Resection was + for metastatic disease. Molecular cytogenetics were + for the mutation in V600E.

Case 4

After recovering from surgery scans showed further PD in the left and right lungs. She was placed on pembrolizumab. Before cycle 2, she told her MD that when she leaned down, she had a severe headache.



Melanoma Brain Mets

- Rapidly evolving
- Cyber knife radiation
- Consider systemic therapy upfront.

What new in 2017

- Staging
  - 1/2018 new AJCC staging
  - Refined T stage
  - Added “c” for nodal stage
  - Added M1d
- Nodal surgery
  - Still best option for local control and staging
  - If completion nodal section is not done, then ultrasound of the nodal basin is needed.

What new in 2017

- Stage III adjuvant therapy
  - Nivolumab was recently shown to improve DFS over high dose ipilimumab in stage IIIB –resected stage IV
  - Consider observation, interferon or nivolumab after a balanced discussion.
- Stage IV paradigms
  - Evolving
  - Consider response and toxicity
- Treatment of brain metastases
  - Challenging and evolving
  - Systemic treatment can be considered upfront

Research

- Treatment after failure of check point inhibitors
- Triple therapy for Targetable tumors
- Brain metastases
- Smart combinations and sequences based on biomarkers and radiographic correlates

Thank you

- UNC Melanoma Program
- New Patient Referrals:
  (by patient's last name)
  - (A-L) Kim Bigelow: 984-974-8468
  - (M-Z) Susie Whorley: 984-974-8289
- Clinical Trials:
  - : 919-966-4432