Malignant Melanoma

Alicia M. Terando, MD
Assistant Professor of Surgery
Department of Surgery
Division of Surgical Oncology
The Ohio State University Wexner Medical Center

Background

- **Melanoma** is a malignancy of pigment-producing cells located predominantly in the skin, but also eyes, ears, GI tract, mucous membranes
- Accounts for 4% of all skin cancers
- Causes the greatest number of skin cancer-related deaths worldwide
- Early detection is the best means of reducing mortality

Incidence Continues to Rise

[Chart showing trends in incidence rates, 1975-2013]
American Cancer Society Statistics - 2017

87,110 estimated new cases (52,170 men and 34,940 women)

9,730 melanoma deaths estimated

Incidence Rates by Race
- Whites: 1:50
- Hispanic: 1:200
- Black: 1:1000

Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun exposure</td>
<td></td>
</tr>
<tr>
<td>UV radiation (320-400 nm)</td>
<td>penetrates deeper into the dermis. Responsible for sun-induced changes in dermal connective tissue and loss of elasticity (wrinkles, signs of aging)</td>
</tr>
<tr>
<td>UVB (290-320 nm)</td>
<td>causes sunburn, induction of increased melanin production in skin</td>
</tr>
<tr>
<td>UVA and UVB carcinogenic</td>
<td>Also found in tanning beds</td>
</tr>
</tbody>
</table>

Sun Exposure

Melanoma: Diagnosis

- Early diagnosis is key to improved outcomes
- ABCDE
  - Asymmetry
  - Border irregularity
  - Color
  - Diameter
  - Evolution


**Asymmetry**

- If you could fold the lesion in half, the 2 halves would not match.

**Border**

Melanoma often has uneven or blurred borders

**Color**

- Melanoma contains mixed shades of tan, brown and black; it can show traces of red, blue or white

**Diameter**

- Melanoma is usually greater than 6 mm (the size of a pencil eraser)
**Evolution** and other suspicious signs

- Changes in appearance, such as spreading of pigment into surrounding skin
- A mole that looks scaly, oozes or bleeds
- Itching, tenderness or pain in a mole
- Brown or black streak under a nail
- Bruise on the foot that does not heal

**ABCD**: asymmetry, borders, color, diameter > 6mm

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**E is for Evolution:**

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**Benign or Malignant??**

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetry</td>
<td></td>
</tr>
<tr>
<td>Border</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>Diameter</td>
<td></td>
</tr>
</tbody>
</table>

Photos Courtesy of the Skin Cancer Foundation
Histologic Subtypes of Melanoma

**Superficial spreading melanoma**
- Most common subtype (~70%)
- Occurs anywhere on the body (non-chronic sun damaged skin)
- Derives its name from histologic evidence of lateral growth for a period of time before vertical growth

**Nodular melanoma**
- Comprise 15-30% of all melanomas
- Discrete nodule with dark black pigmentation is typical clinically
- Present with clinical and histologic evidence of vertical growth only

**Lentigo maligna melanoma**
- ~ 5% of melanomas
- Arises from *in situ* melanoma on sun-damaged skin
- Usually head or neck

**Acral lentiginous**
**Acral Lentiginous Melanoma**

- ~ 2-10% of melanomas
- Most common subtype in dark-skinned individuals
- Involves palms, soles, and nail beds
- More aggressive than other types – ? due to depth at diagnosis

**Mucosal Melanoma - where the “sun don’t shine”**

- Rare, but can occur on almost any mucosal surface
- 2x higher in whites vs blacks
- Head/neck (ie nasal, sinus, mouth), female genital tract, anorectal region, urinary tract

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**Melanoma: Diagnosis**

**Excisional biopsy** (elliptical, punch, or saucerization): 1-3 mm margin, avoid larger margin to permit accurate lymphatic mapping

**Full thickness incisional or punch:** attempt to perform in clinically thickest portion of lesion

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**Evaluation of Patients with Newly Diagnosed Melanoma**

**Pathology**
- Breslow depth
- Ulceration
- Mitotic rate
- Satellites?
- Status of the deep margin – important for thin melanoma

**Physical Exam**
- Size and location of the lesion?
- Residual pigment?
- Satellites?
- Palpable or suspicious nodes?
**Melanoma: surgical care**

Wide excision of the primary lesion

Nodal assessment

**Surgical Margins**

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>≤ 1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01 – 2 mm</td>
<td>1 – 2 cm</td>
</tr>
<tr>
<td>2.01 – 4 mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>&gt; 4 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

Margins of >2cm do not improve rate of local recurrence, disease-free survival, or overall survival, but they do increase the risk of requiring a skin graft or flap closure of the defect.

**Wide excision with Primary Closure**

Length = 3-4 x Width

**Skin graft**

[Image of skin graft and closure process]
Local Tissue Rearrangement

Facial Reconstruction
Facial Reconstruction

Ear Reconstruction
How and When to Manage the Draining Lymph Node Basin

Elective Versus Therapeutic Lymph Node Dissection

Therapeutic lymph node dissection “watch and wait”
– Delayed until the time of nodal recurrence
– Avoided LND complications in node-negative patients.
– Strategy assumes there will be no evidence of distant metastatic disease at the time of nodal recurrence – not necessarily
Elective Versus Therapeutic Lymph Node Dissection

<table>
<thead>
<tr>
<th>Elective</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>“search and destroy”</td>
<td>• Avoid complications from node dissection in node negative patients</td>
</tr>
<tr>
<td>• Performed at the time of WLE.</td>
<td>• Decrease risk of local failure</td>
</tr>
<tr>
<td>• 80% of patients were node-negative.</td>
<td>• Potentially allowing greater opportunity for metastatic spread</td>
</tr>
<tr>
<td>• Survival advantage in retrospective studies.</td>
<td>• Subjecting node negative patients to surgical morbidity</td>
</tr>
</tbody>
</table>

Therapeutic vs. Elective Lymph Node Dissection

<table>
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<tr>
<th>Therapeutic</th>
<th>Elective</th>
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</thead>
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<tr>
<td>• Avoid complications from node dissection in node negative patients</td>
<td>• Subjecting node negative patients to surgical morbidity</td>
</tr>
<tr>
<td>• Risk of local failure</td>
<td>• Decrease risk of local failure</td>
</tr>
<tr>
<td>• Potentially allowing greater opportunity for metastatic spread</td>
<td>• Some patients will develop metastatic disease without nodal disease</td>
</tr>
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</table>

Revolution circa 1994: Sentinel lymph node biopsy

- Developed by Dr. Donald Morton at the John Wayne Cancer Center in Los Angeles
- Identify the first draining lymph node
- If the sentinel node is negative – extremely unlikely that there is any disease in the nodal basin
- If the sentinel node is positive – completion lymph node dissection
- Reserve lymphadenectomy for the patients who really need it

Video: Injection and Lymphoscintigraphy

[Image of a medical procedure]
When do we do Sentinel Lymph Node Biopsy?

- NCCN recommendations:
  - SLN biopsy for patients with melanoma > 1mm regardless of characteristics. Standard of care.
  - For lesions 0.75-1.0 mm, consider SLN biopsy if there are aggressive features such as:
    - Ulceration
    - Clark level IV or V
    - (Satellitosis)
    - (Regression)
    - (Young Age)
    - (High Mitotic Rate)

  Some consider SLNbx for these, too

The Case for Sentinel Lymph Node Biopsy

- Better pathologic examination
- Powerful predictor of survival
- Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal Recurrence
- Avoid complications from ELND for node negative patients
- Survival benefit to SLNBx?
Increased cross-sectional area examined with serial sectioning.

- 1 cm
- 1.5 mm
- 1 cm

94 mm³

134.9 mm³


The Case for Sentinel Lymph Node Biopsy

Better pathologic examination
Powerful predictor of survival
Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence
Avoid complications from ELND for node negative patients
Survival benefit to SLNBx?

IHC in Sentinel Lymph Node Biopsy

SLN status is the most powerful independent prognostic factor predicting survival, individualizing treatment.

Gershenwald et al, J Clin Oncol 1999
The Case for Sentinel Lymph Node Biopsy

Better pathologic examination
Powerful predictor of survival

Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence

Avoid complications from ELND for node negative patients

Survival benefit to SLNBx?

Avoid Regional Nodal Failure

Lymphedema

http://www.medsci.org/v07p0353/ijmsv07p0353g02.jpg
The Case for Sentinel Lymph Node Biopsy

Better pathologic examination
Powerful predictor of survival
Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence
Survival benefit to SLNBx?

Multicenter Selective Lymphadenectomy Trial -I

Comparing:
- wide excision alone
- wide excision + sentinel lymph node biopsy

1.2 – 3.5 mm thickness cutaneous melanoma

Wide local excision with Lymphatic mapping
Wide local excision Alone

SLN Positive
Perform Lymphadenectomy

SLN Negative
Follow for Survival

Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma

**MSLT-1 Results**

- 2001 Patients with primary melanoma
- Wide excision alone vs wide excision + SLN biopsy
- Overall, no difference in 10 year melanoma specific survival
- Among node positive patients (either sentinel node positive or nodal recurrence during observation) 10 year melanoma specific survival:
  - Sentinel node bx: 62.1%
  - Observation (w/e alone): 41.5%

**Multicenter Selective Lymphadenectomy Trial - II**

- + SLNbx patients randomized to CLND vs nodal observation (with clinical examinations and ultrasound) to determine if CLND improves relapse rate or survival

**MSLT-II Results**

- 1934 patients node positive, intermediate thickness melanoma
- Randomized to completion lymph node dissection or nodal observation with ultrasonography
- 3-year Melanoma Specific Survival Similar
- 3-year Disease-Free Survival slightly higher in dissection group (68% vs 63%)
- Lymphedema 24% in dissection group vs 6% in the observation group
Management of Positive Lymph Nodes

Positive Sentinel Node – Observation

Palpable Lymph Node in a patient with a primary melanoma, or a history of melanoma
• FNA to get a tissue diagnosis
• If confirmed to be melanoma, staging work-up indicated to rule out distant metastatic disease
• If no distant disease, lymph node dissection

Melanoma

Kari Kendra, MD, PhD
Associate Professor of Internal Medicine
Department of Internal Medicine
Division of Medical Oncology
The Ohio State University Wexner Medical Center

Metastatic Disease

Case 1

25 y/o male:
- Presents with SOB
- Exam: left axillary mass
- CT: bilateral pulmonary nodules, liver nodules, and left axillary mass
- PMH: stage IIb melanoma, left arm, resected
- Biopsy of axillary mass: melanoma

What is his prognosis?
What treatments are available?
Recurrence melanoma: Treatment

Localized

- Surgery – isolated metastases, limited in size and number, rendered disease free
- Radiation – CNS lesions, cord compression, pain control
- Tvec (attenuated oncolytic HSV that contains GMCSF) – lesions accessible to injection

T-VEC
Talimogene laherparepvec

FDA approved as monotherapy for localized treatment of unresectable cutaneous, subcutaneous, and nodal lesions.

- ORR 26%
- Durable response rate 16.3%
- Median overall survival 23.3 mo (Annals of Pharmacotherapy, 2017)

Administration
- Initial injection – 1 x 10(6) PFU/mL, up to 4 mL
- Second injection (3 weeks) – 1 x 10(8) PFU/mL, up to 4 L
- Subsequent injections (q2 weeks) – 1 x 10(8) PFU/mL, up to 4 mL
Case 1

25 y/o male:
- Presents with SOB
- Exam: left axillary mass
- CT: bilateral pulmonary nodules, liver nodules, and left axillary mass
- PMH: stage IIb melanoma, left arm, resected
- Biopsy of axillary mass: melanoma (BRAF V600e mutation present)

This patient has widespread disease.
Which systemic treatment to use?

Metastatic melanoma

Systemic therapy:
- **Chemotherapy** – targets rapidly cycling cells
- **Immunotherapy** – activates the immune system to recognize and destroy the cancer
- **Targeted therapy** – for tumors with specific mutations

Other targeted therapies (under investigation)

- C-kit
  - Imatinib (Gleevec)
- NRAS
  - Trametinib
- C-Met
  - Crizotinib
  - Cabozantinib

Mechanism of action: immunotherapies
Activated dendritic cells (Antigen Presenting Cells)

Regulation of T cell activation is a Complex Process

Activated T cell
- IL-2 secretion
- Proliferation
- Effector function
- Induction of CTLA-4

CTLA-4: B7 suppression
Termination of response

Antigen-specific T cell Activation
- TCR: Antigen-MHC
- CD28: B7 Co-stimulation

Ipilimumab

Survival Rate

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab + gp100</th>
<th>Ipilimumab alone</th>
<th>Gp100 alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>44%</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>2-year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>
Immune-related Adverse Events associated with ipilimumab
- Rash
- Colitis/enteritis
- Transaminitis
- Thyroiditis
- Adrenal insufficiency
- Hypophysitis

Hodi et al, NEJM, 2010

Ipilimumab toxicities

Weber et al, JCO, 2012

Metastatic disease: Ipilimumab

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate improved over chemotherapy</td>
<td>Delayed onset of response</td>
</tr>
<tr>
<td>Durable responses</td>
<td>Toxicities</td>
</tr>
<tr>
<td>Limited treatment duration</td>
<td>Response rate not high enough</td>
</tr>
</tbody>
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Ipilimumab

<table>
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<td>2-year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>
Mechanism of action: immunotherapies

- Anti-CTLA4:
  - Ipilimumab
- Anti PD1
  - Nivolumab
  - Pembrolizumab

Nivolumab

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n=120)</th>
<th>ICC (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>38 (31.7%)</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4 (3.3%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>34 (28.3%)</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>SD</td>
<td>28 (23.2)</td>
<td>16 (34.0%)</td>
</tr>
<tr>
<td>PD</td>
<td>42 (35.0%)</td>
<td>15 (31.9%)</td>
</tr>
<tr>
<td>unable to establish</td>
<td>12 (12.0%)</td>
<td>11 (23.4%)</td>
</tr>
</tbody>
</table>

Weber et al, Lancet 2015

Larkin et al, JCO 2017
**PD-1 blockade:** pembrolizumab, nivolumab

**Advantages**
- Low toxicity profile
- Increased response rate
- More rapid response
- Durable response

**Disadvantages**
- Duration of treatment is unknown
- Cost
- Unexpected autoimmune toxicities

**Systemic therapies for metastatic disease**

**Immunotherapies**
- Single agent
  - Ipilimumab
  - Nivolumab
  - Pembrolizumab
  - IL2

**Targeted therapies**
- BRAFi
  - Dabrafenib
  - Vemurafenib
- MEKi
  - Trametinib
  - Cobimetinib

**Phase 3 trial of Nivo + Ipi vs Nivo vs Ipi**

- Media PFS
  - N+I: 11.5 mo
  - I: 6.9 mo
- PFS at 2 yr:
  - N+I: 43%
  - N: 37%
  - I: 12%

**Immunotherapies**

- Pembrolizumab vs Ipilimumab
  - Phase 3 randomized, open-label
  - N=834
  - Schachter et al, Lancet 2017

- Overall Survival
- Progression-Free Survival
- Response

- Pembrolizumab every 2 weeks
- Pembrolizumab every 3 weeks
- Ipilimumab
Mechanism of action:
targeted therapies

Huang, PH, Marais R. Nature 2009;459;336-337

Objective Responses with vemurafenib

N= 132
- ORR 53%
- CR 6%
- PR 47%
- Median duration of response 6.7 mo
- Responses: M1a, M1b, M1c
- The majority with > 30% decrease in change from baseline (RECIST)

Sosman et al, 2012
Inhibition of the BRAF pathway

<table>
<thead>
<tr>
<th></th>
<th>Single agent (dabrafenib) (N=211)</th>
<th>Combination (dabrafenib/trametinib) (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>18.8 mo</td>
<td>25.1 mo</td>
</tr>
<tr>
<td>1 yr OS</td>
<td>68%</td>
<td>74%</td>
</tr>
<tr>
<td>2 yr OS</td>
<td>42%</td>
<td>51%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.8 mo</td>
<td>11.0 mo</td>
</tr>
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</table>

Long et al, Lancet 2015

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<th>Combination (dabrafenib/trametinib) (n=212)</th>
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</thead>
<tbody>
<tr>
<td>3-year PFS</td>
<td>12%</td>
<td>22%</td>
</tr>
<tr>
<td>3-year OS</td>
<td>12%</td>
<td>32%</td>
</tr>
</tbody>
</table>

(58% of those alive at 3 yrs remained on combination therapy)

Long et al, Ann Oncol 2017

Dabrafenib

Adverse events
- Peripheral edema (17 – 31%)
- Dermatologic
  - Alopecia (22%)
  - Hand-foot syndrome (21%)
  - Hyperkeratosis (37%)
  - Night sweats (6 – 24%)
  - Papillomas (29%)
  - Rash (17-53%)
- Endocrine
  - Hyperglycemia (50%)
  - Hypokalemia/hypophosph.
- GI
  - Abdominal pain, constipation/diarrhea, N/V
- Hematologic
  - Anemia, leukopenia, neutropenia, thrombocytopenia
- Hepatic
- Musculoskeletal
  - Arthritis
  - myalgia
- Other
  - Fatigue, fever, rigors

Flaherty et al NEJM 2012

Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib</th>
<th>Dabrafenib/trametinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>32%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28%</td>
<td>51%</td>
</tr>
<tr>
<td>Chills</td>
<td>16%</td>
<td>30%</td>
</tr>
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Flaherty et al NEJM 2012
Case 1

25 y/o male:
- Presents with SOB
- Exam: left axillary mass
- CT: bilateral pulmonary nodules, liver nodules, and left axillary mass
- PMH: stage IIB melanoma, left arm, resected
- Biopsy of axillary mass: melanoma (BRAF V600e mutation present)

*What is this patient’s prognosis?*
*Which systemic treatment to use?*

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**Immunotherapy**
- **Pros**
  - Durable responses
  - RR: 40 – 55%
  - Median OS > 2 years
- **Cons**
  - Increased risk of immune mediated events

**Targeted therapy**
- **Pros**
  - Rapid response rate
  - Combination RR 70%
  - Median OS > 2 years
- **Cons**
  - 50% of responders develop resistance in 13 months

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Patients prognosis is changing. The recently approved therapies have had significant impact on the duration and quality of life for some.

Treatment options:
- Immunotherapies vs targeted therapies, where to start?
Clinical trials

Metastatic disease
- E6613M “A randomized phase II trial of dabrafenib + trametinib followed by ipilimumab and Nivolumab at progression vs ipilimumab + Nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAF V600e mutant melanoma”
- EA131 “Molecular Analysis for Therapy Choice (MATCH)”
- S1320 “A randomized, phase II trial of intermittent vs continuous dosing of dabrafenib and trametinib in BRAFV600E/K mutant melanoma”
- OSU 13124 “a phase 1 expansion cohort evaluating the selective inhibitor of nuclear export (SINE) KPT-330 in patients with unresectable melanoma.”
- OSU 17090 “a phase II study of ibrutinib in refractory distant metastatic cutaneous melanoma: correlation of biomarkers with response and resistance.”

Case 2

34 y/o female presented with a bleeding mole on her arm.
- **Biopsy:** nodular melanoma, 4.1 mm deep, with ulceration, mitotic rate 15/10 HPF
- **Wide excision:** no residual tumor
- **Sentinel Node:** positive for 2/2 LN, with extracapsular extension in 1 LN
- **Axillary LN dissection:** 0/20 LN

What is the next step?

Prognostic indicators

- Thickness (Breslow depth)
- Nodal status
- Ulceration
- Satellite lesions
- In transit lesions
Case 1

Our 34 y/o female has multiple poor prognostic indicators:

- Depth > 1.0 mm
- Lymph nodes positive (macroscopic)
- Ulceration present
- Mitotic rate high

Adjuvant therapy for high risk patients

What therapies are available?
How do we identify patients for treatment?

Systemic Therapy:

Adjuvant

- FDA approved biologic agents
  - IFN (1 year)
  - Pegylated IFN (5 years)
  - Ipilimumab (10 mg/kg, 3 year)
- Data available, not yet FDA approved
  - Nivolumab (1 year)
- Data pending from large clinical trials
  - Ipilimumab (3 mg/kg, 1 year)
  - Pembrolizumab (200 mg, fixed dosing)
**Adjuvant radiation**

- Adjuvant radiation
  - Dose: 30 Gy in 6 Gy fractions 2 times/week
  - Improvement in local, regional and locoregional disease control
  - No impact on OS or RFS

**Adjuvant therapy with Interferon Alfa-2b (E1684)**

FDA approved

- IFN-alpha 2b for adjuvant treatment of melanoma patients with thick primary tumors (>4mm) or resected nodal disease

Kirkwood et al, JCO 1996;14:7

**Patient population**

- Breslow's depth >4mm
- LN+ after ELND
- Clinical LN+ with synchronous primary
- Regional LN recurrence after surgery for primary

Kirkwood et al, JCO 1996;14:7

**Treatment**

- **High-dose IFNα-2b**: 20 MU/m² IV, 5 days per week for 4 weeks (induction phase) followed by 10 MU/m² SC TIW for 48 weeks (maintenance)
- Observation
Adjuvant therapy with Interferon Alfa-2b (E1684)

### Cochrane meta-analysis of IFN alpha adj trials

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>RFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.83 (0.78 – 0.87)</td>
<td>0.91 (0.85-0.97)</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>NNT</td>
<td>16</td>
<td>33</td>
</tr>
</tbody>
</table>

**Notes:**
- RFS: relapse-free survival
- OS: overall survival
- HR: hazard ratio
- NNT: number needed to treat to prevent one event

Mocellin et al, 2013

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### Adjuvant therapy with Interferon Alfa-2b (E1684)

**TOXICITIES:**
- constitutional
- myelosuppression
- hepatotoxicity
- neurologic

- 67% of all patients had severe (grade 3) toxicity at some point during treatment
- Supportive care is necessary

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### Adjuvant Ipilimumab

**Ipilimumab (10 mg/kg):**
- Stage III melanoma
- Reduced risk of relapse (HR 0.76)
- Improved OS (HR 0.72)
- 5 year recurrence-free survival of 40.8% (placebo 30.3%)

**Toxicities:**
- Immune related toxicities remain high

Adjuvant Ipiilimumab
(10 mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Ipiilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>234/475</td>
<td>294/476</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.75 (0.64 – 0.90)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0013</td>
<td></td>
</tr>
<tr>
<td>1 yr RFS</td>
<td>63.5%</td>
<td>56.1%</td>
</tr>
<tr>
<td>2 yr RFS</td>
<td>51.5%</td>
<td>43.8%</td>
</tr>
<tr>
<td>3 yr RFS</td>
<td>46.5%</td>
<td>34.8%</td>
</tr>
</tbody>
</table>

Eggermont et al, Lancet Oncol 2016

Adjuvant nivolumab

- Randomized, double blinded, phase 3 trial
- N=906
- Stage IIIB, IIIC, or IV – NED from surgical resection
- Nivolumab 3 mg/kg every 2 weeks x 1 year vs Ipiilimumab 10 mg/kg every 3 weeks for 4 doses, then every 12 weeks for 1 year

Weber et al, NEJM 2017

Adjuvant nivolumab

Nivolumab vs Ipiilimumab

- Relapse free survival: HR 0.65 (97.56% CI, 0.51 – 0.83) p< 0.001
- PDL1 < 5% HR 0.71 (95% CI, 0.56 – 0.91)
- PDL1 > 5% HR 0.50 (95% CI, 0.32 – 0.78)

Weber et al, NEJM 2017

Adjuvant Nivolumab

Nivolumab vs Ipiilimumab

Recurrence free survival:

- Stage IIIB or IIIC - Hazard ratio 0.64 (95% CI, 0.52 – 0.82)
- Stage IV – Hazard ratio 0.70 (95% CI, 0.45 – 1.10)

Weber et al, NEJM 2017
Adjuvant ipi vs nivo: treatment related adverse events

**Ipilimumab (10 mg/kg)**
- Grade 3 or 4 – 45.9%
- Treatment related AE leading to discontinuation – 30%

**Nivolumab (3 mg/kg)**
- Grade 3 or 4 – 14.4%
- Treatment related AE leading to discontinuation – 4.6%

**AE > 2%**
- Diarrhea (9.9%)
- Increase ALT (5.7%)
- Increase AST (4.2%)
- Rash (3.1%)
- Hypophysitis (2.4%)
- Maculopapular rash (0.2%)

Weber et al, NEJM 2017

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Adjuvant BRAF inhibitors

Double blind, placebo-controlled, randomized phase 3 trial
- Eligibility:
  - Stage III
  - BRAF V600E or V600K mutations
- 2 arms:
  - Dabrafenib (150 mg po bid) + trametinib (2 mg po qd) (n=438)
  - Placebo (n = 432)

Long et al, NEJM 2017

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Dabrafenib + Trametinib vs placebo

- Relapse free survival
  - HR for relapse 0.47 (95% CI, 0.39 – 0.58)
- Overall survival
  - HR for death 0.57 (95% CI, 0.42 – 0.79)

Long et al, NEJM 2017

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Dabrafenib + Trametinib vs placebo

- Combination therapy was favored in all subgroups
  - Male/female
  - Age <65/>65
  - Disease stage: IIIa, IIIb, IIIc
  - LN involvement: micrometastasis, macrometastasis
  - Ulceration present/absent
  - Number of nodal mets

Long et al, NEJM 2017
### Dabrafenib + Trametinib vs placebo

<table>
<thead>
<tr>
<th>AE (&gt;20%)</th>
<th>Combination therapy</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>none</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Nausea</td>
<td>Headache</td>
</tr>
<tr>
<td>Nausea</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Long et al, NEJM 2017*

### Case 2

34 y/o female presented with a bleeding mole on her arm.
- **Biopsy**: nodular melanoma, 4.1 mm deep, with ulceration, mitotic rate 15/10 HPF
- **Wide excision**: no residual tumor
- **Sentinel Node**: positive for 2/2 LN
- **Axillary LN dissection**: 0/20 LN

*What adjuvant therapy options are available?*

### Adjuvant systemic therapy

**FDA approved**
- Interferon
- Pegylated interferon
- Ipilimumab

**Data just released**
- Nivolumab
- Dabrafenib/Trametinib

**Data pending**
- IFN vs LD Ipi vs HD Ipi for 1 year
- Physician choice vs pembrolizumab for 2 yr

### Fifteen-year survival curves comparing localized melanoma (stages I and II), regional metastases (stage III), and distant metastases (stage IV)

Improvements in outcomes have been significant:
- but there are many who still do not respond
- many develop resistance
- costs to the health care system are high

Further research needs to continue.

Thank you!
- to all the patients who participated in the clinical trials
- to all the researchers who contributed their ideas
- to all the funding agencies that made these advancements possible