Malignant Melanoma

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The Ohio State University Wexner Medical Center

Malignant Melanoma

CDC/ Carl Washington, M.D., Emory Univ. School of Medicine; Mona Saraiya, MD, MPH

Image courtesy of Library of congress
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

*Trends in incidence rates, 1975-2013*
Melanoma of the skin, by sex

Per 100,000, age adjusted to the 2000 US standard population.
Data sources: Surveillance, Epidemiology, and End Results (SEER) registries, National Cancer Institute, 2016
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

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**Risk Factors**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Estimated relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk traits</td>
<td></td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>1000</td>
</tr>
<tr>
<td>Dysplastic nevi, prior melanoma, and familial melanoma</td>
<td>500</td>
</tr>
<tr>
<td>Dysplastic nevi, no prior melanoma, and familial melanoma</td>
<td>148</td>
</tr>
<tr>
<td>Dysplastic nevi, no FHM or FHP of melanoma</td>
<td>3-27</td>
</tr>
<tr>
<td>Many nevi (≥50)</td>
<td>7-54</td>
</tr>
<tr>
<td>Caucasian (e.g., African American)</td>
<td>15-20</td>
</tr>
<tr>
<td>Congenital melanocytic nevi (especially large nevi)</td>
<td>17-23</td>
</tr>
<tr>
<td>Personal history of melanoma</td>
<td>9</td>
</tr>
<tr>
<td>Cutaneous melanoma in first-degree blood relative</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Estimated relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk traits</td>
<td></td>
</tr>
<tr>
<td>De novo sun-induced freckles</td>
<td>3-20</td>
</tr>
<tr>
<td>Prior history of NMSC</td>
<td>3-17</td>
</tr>
<tr>
<td>Infections</td>
<td>2-8</td>
</tr>
<tr>
<td>Other phenotypic traits: red hair, blond hair, blue eyes</td>
<td>1-6</td>
</tr>
<tr>
<td>History of severe and painful sunburns</td>
<td>1-6</td>
</tr>
<tr>
<td>Sun sensitivity, relative inability to tan</td>
<td>1-5</td>
</tr>
</tbody>
</table>

*PH, personal history. **PH, familial history.

Sun Exposure

UVA radiation (320-400 nm) - penetrates deeper into the dermis. Responsible for sun-induced changes in dermal connective tissue and loss of elasticity (wrinkles, signs of aging)

UVB (290-320 nm) - causes sunburn, induction of increased melanin production in skin

UVA and UVB carcinogenic

Also found in tanning beds

Melanoma: Diagnosis

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

Image source: FDA, Radiation-emitting Products, Ultraviolet Radiation (February 2010).
Asymmetry

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

Benign  Malignant

Photos Courtesy of the Skin Cancer Foundation

Border

Melanoma often has uneven or blurred borders

Benign  Malignant

Photos Courtesy of the Skin Cancer Foundation
**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

E is for Evolution:


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

<table>
<thead>
<tr>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading melanoma</td>
</tr>
<tr>
<td>Nodular melanoma</td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
</tr>
<tr>
<td>Acral lentiginous melanoma</td>
</tr>
</tbody>
</table>

**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

![Nodular melanoma](image)

### Lentigo maligna melanoma

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

![Lentigo maligna melanoma](image)
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
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

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

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**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>$\leq 1$ 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


www.eatonhand.com
Local Tissue Rearrangement

ANZ J. Surg. 2003;73: 112–120;

Local Tissue Rearrangement
Local Tissue Rearrangement

Facial Reconstruction
Facial Reconstruction

Facial Reconstruction
Ear 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

Elective lymph node dissection
“search and destroy”
– Performed at the time of WLE.
– 80% of patients were node-negative.
– Survival advantage in retrospective studies.

Therapeutic vs. Elective Lymph Node Dissection

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

Video: Surgical Sentinel Lymph Node Biopsy
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)

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.


IHC in Sentinel Lymph Node Biopsy
The Case for Sentinel Lymph Node Biopsy

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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?

Prognosis Associated with Sentinel Node Status

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

Disease-free survival stratified by SLN status

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
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?

Lymphedema

http://www.medsci.org/v07/p0353/jmsv/v07p0353p02.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
Multicenter Selective Lymphadenectomy Trial -I

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

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The NEW ENGLAND JOURNAL of MEDICINE

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%

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**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
Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma


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

Recurrent 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

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

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

CTLA-4 : B7 suppression
Termination of response
**Ipilimumab**

<table>
<thead>
<tr>
<th>Survival Rate</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>46%</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

Advantages
- Response rate improved over chemotherapy
- Durable responses
- Limited treatment duration

Disadvantages
- Delayed onset of response
- Toxicities
- Response rate not high enough

Ipilimumab

<table>
<thead>
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<tr>
<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>
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</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 (10.0%)</td>
<td>11 (23.4%)</td>
</tr>
</tbody>
</table>

Weber et al, Lancet 2015

Nivolumab

![Graph showing PFS (Progression-Free Survival) vs Time (months)]

<table>
<thead>
<tr>
<th>No. of patients at risk</th>
<th>NIVO</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>272</td>
<td>133</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>59</td>
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<tr>
<td>15</td>
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<tr>
<td>36</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>39</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

Larkin et al, JCO 2017
Pembrolizumab vs Ipilimumab

Phase 3 randomized, open-label
N=834

- Pembrolizumab every 2 weeks
- Pembrolizumab every 3 weeks
- Ipilimumab

Schachter et al, Lancet 2017

Overall Survival

Progression-Free Survival

Response

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
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%

Wolchok et al, NEJM 2017

Systemic therapies for metastatic disease

**Immunotherapies**
- Single agent
  - Ipilimumab
  - Nivolumab
  - Pembrolizumab
  - IL2
- Combination
  - Ipi/nivo

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

## Inhibition of the BRAF pathway

<table>
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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 (20%)
  - Hyperkeratosis (37%)
  - Night sweats (6 – 24%)
  - Papilloma (27%)
  - Rash (17-53%)
- Endocrine
  - Hyperglycemia (50%)
  - Hypokalemia/hypophosph.
- GI
  - Abdominal pain, constipation/diarrhea, N/V
- Hematologic
  - Anemia, leukopenia, neutropenia, thrombocytopenia
- Hepatic
- Musculoskeletal
  - Arthralgia
  - Myalgia
- Other
  - Fatigue, fever, rigors

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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>
</tbody>
</table>

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?*

Ugurel et al, Eur J of Cancer, 2017
Case 1

- 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?

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy</td>
<td>Increased risk of immune mediated events</td>
</tr>
<tr>
<td>Durable responses</td>
<td></td>
</tr>
<tr>
<td>RR: 40 – 55%</td>
<td></td>
</tr>
<tr>
<td>Median OS &gt; 2 years</td>
<td>50% of responders develop resistance in 13 months</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td></td>
</tr>
<tr>
<td>Rapid response rate</td>
<td></td>
</tr>
<tr>
<td>Combination RR 70%</td>
<td></td>
</tr>
<tr>
<td>Median OS &gt; 2 years</td>
<td></td>
</tr>
</tbody>
</table>
Clinical trials

Metastatic disease

- EA6134 “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 BRAF V600e/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
Case 2

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

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

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
Adjuvant therapy with Interferon Alfa-2b (E1684)

- Patient population
  - Breslows depth >4mm
  - LN+ after ELND
  - clinical LN+ with synchronous primary
  - regional LN recurrence after surgery for primary

Kirkwood et al, JCO 1996;14:7

Adjuvant therapy with Interferon Alfa-2b (E1684)

**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)

<table>
<thead>
<tr>
<th></th>
<th>IFNα-2b</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>median DFS</td>
<td>1.7 yr</td>
<td>1.0 yr</td>
</tr>
<tr>
<td>OS</td>
<td>3.8 yr</td>
<td>2.8 yr</td>
</tr>
</tbody>
</table>

* benefit greatest in LN+ patients

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></td>
<td>10,345 subjects (17 trials)</td>
<td>9927 subjects (15 trials)</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>

RFS relapse free survival, OS overall survival, HR hazard ration, NNT number needed to treat to prevent one event

Mocellin et al, 2013
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

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 Ipilimumab**  
*(10 mg/kg)*

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</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

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**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
  - Ipilimumab 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 Ipilimumab

- 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)

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Adjuvant Nivolumab

Nivolumab vs Ipilimumab

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)
**Adjuvant ipi vs nivo:**
treatment related adverse events

<table>
<thead>
<tr>
<th><strong>Ipilimumab (10 mg/kg)</strong></th>
<th><strong>Nivolumab (3 mg/kg)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 – 45.9%</td>
<td>Grade 3 or 4 – 14.4%</td>
</tr>
<tr>
<td>Treatment related AE leading to discontinuation – 30%</td>
<td>Treatment related AE leading to discontinuation – 4.6%</td>
</tr>
</tbody>
</table>

**AE > 2%**
- Diarrhea (9.5%)
- Increase ALT (5.7%)
- Increase AST (4.2%)
- Rash (3.1%)
- Hypophysitis (2.4%)
- Maculopapular rash (2.0%)

**AE >2% (none)**
- Diarrhea (1.5%)
- Increase ALT (1.1%)
- Increase AST (0.4%)
- Rash (1.1%)

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
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

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></td>
<td>Nausea</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>Headache</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>
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</tbody>
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*Long et al, NEJM 2017*

### Case 2

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*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