Melanoma Update 2017

Key issues you need to know

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY
Darrell S, Rigel, MD
Melanoma Update – 2017
Key issues you need to know
Castle – A, H, I

Key issues in Melanoma
✓ Epidemiology
✓ Risk Factors
✓ Prevention
✓ Management
✓ Genetics
  - Diagnosis
  - Prognosis
  - Advanced disease therapy

Epidemiology:
Incidence and Mortality

Cancer USA - 2017

More Skin Cancers than all other cancers combined

Skin Cancer USA - 2017

Melanoma: 87,110
NMSC (BCC, SCC): 2,900,000

More Skin Cancers than all other cancers combined
Melanoma – US 2017

- Invasive = 87,100
- In-situ = 63,410

US Cancer Statistics, 2017

US Annual Deaths from Melanoma
Skin Cancer Deaths US - 2017

Over 1 American dies of Melanoma every hour

Key issues in Melanoma

Risk Factors

Who gets Melanoma?

Melanoma in Non-Caucasians

Melanoma Presentation Stage by Race

Five-Year Relative Survival Rates by Stage at Diagnosis and Race US 2006 to 2012
**MM incidence in transplant pts**

- Review of 3 studies of MM risk in transplant pts
- Significantly increased MM risk from 2.6-8x

**Conclusions:**
- Patients who have thin MMs removed prior to organ transplantation appear to not be at increased risk of recurrence following transplantation.
- Immunosuppressive medications taken by OTRs appear to predispose to de novo melanoma and are associated with worse outcomes in thicker tumors.
- Cases of donor-derived MM underline the need for careful donor selection and exclusion of MM prior to transplantation

Faisal et al, J Skin Cancer, 2012

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**Recurring Melanoma in Women <50 Years of Age**

**Risk Factors**

- 462 females 49 years old and less with hx of MM were studied
- 41 patients with a pregnancy-associated melanoma were 9 times more likely to have recurrence than non-pregnant patients, as well as a 7-fold increase in metastasis and 5-fold increase in mortality
- Positive sentinel node status, recurrence rates, metastatic disease, and death rates were greater for women 40 to 49 year of age.

**Conclusions:**
- Women who are diagnosed with melanoma during pregnancy or within 1 year after childbirth should be followed more closely for recurrence
- Women less than age 50 should have their skin checked regularly and conduct self-exams


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**Skin Cancer in Psoriasis Treated with Phototherapy**

- Retrospective study; 92 patients
- Treated with PUVA or nb-UVB for 1-28 years (mean: 7.1)
- PUVA = 9 skin cancers (1 MM, 7 BCC, 1 SCC) = 4.7%
- nb-UVB = 14 skin cancers (2 MM, 4 BCC, 8 SCC) = 12%

**Conclusion:**
- Risk-benefit evaluation needed before UV tx
- Careful monitoring for skin cancer during and after UV tx

Maizano A et al, J Dermatolog Treat. 2016

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**MM and Parkinson Disease**

- Literature Review
- PD = overall decreased risk of cancer
- PD = increased risk w/ breast ca and MM
- Family Hx, light hair and skin color = higher risk

**Conclusion:**
- Link between PD and MM exists, likely multifactorial involving genetic and environmental risk factors


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**Coffee Reduced MM Risk – Meta-Analysis**

- Meta-Analysis: 2 case-control and 5 cohort
- Pooled RR of MM = 0.81 (95%CI=0.68-0.97)
  - Highest vs. Lowest consumers of coffee
- Dose Response: RR of MM = 0.955 (95%CI=0.91-0.99)
- Decaf = no association

**Conclusion:**
- Caffeinated coffee may have chemo-preventive effects against MM


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**Coffee and MM: meta-analysis**

- Meta-analysis: 23 studies; 2,268,338 participants
- Compared to lowest level consumption, RR= :
  - Total coffee = 0.8
  - Caffeinated coffee = 0.85
  - Decaf coffee = 0.92
- Dose-Response MM risk decreased for each 1 cup/day
  - 3% decrease for all coffee
  - 4% decrease for caffeinated coffee

**Conclusion:**
- Coffee may reduce risk of MM

**PDE-5 Inhibitors (Viagra) and Risk of Melanoma**

- Swedish Registry; 4065 melanoma cases vs controls
- Increased risk of MM in men taking PDE5 inhibitors OR 1.21 95% CI=1.08-1.36
- Greatest risk increase in men who filled single script, NOT significant among men with multiple scripts
- Associated with increased risk of BCC
- **Conclusion:**
  - PDE5-I use associated with increased risk of MM & BCC

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**Sildenafil use and increased risk of incident MM in US men: A prospective cohort study**

- Sildenafil is a phosphodiesterase (PDE) 5A inhibitor
- Recent studies have shown that BRAF activation down-regulates PDE5A levels, and low PDE5A expression by BRAF activation or sildenafil use increases the invasiveness of MM cells, which raises the possible adverse effect of sildenafil use on MM risk.
- Recent sildenafil use at baseline was significantly associated with an increased risk of subsequent MM with a multivariate HR=1.84
- Ever use of sildenafil was also associated with a higher risk of MM (HR=1.92)
- Erectile function itself was not associated with an altered risk of melanoma.
- **Conclusions:**
  - Sildenafil use may be associated with an increased risk of developing MM but more studies need to be done to verify

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**Geographic impact on MM incidence**

- 16-year prospective study of 1171 Australian men and women
- Examined height, BMI, incidence of skin cancer
- BMI and BSA were NOT related to skin cancer incidence
- After adjusting for skin phenotype, sun exposure and chronic photodamage:
  - Height >175cm (5’9”) associated with SCC in men, BCC in women
  - Melanoma and height trended in men
- **Conclusion:**
  - After adjusting for sun exposure, tall stature may be risk factor for skin cancer

---

**Body size and Height risk for Skin Cancer?**

- Examined height, BMI, incidence of skin cancer
- BMI and BSA were NOT related to skin cancer incidence
- After adjusting for skin phenotype, sun exposure and chronic photodamage:
  - Height >175cm (5’9”) associated with SCC in men, BCC in women
  - Melanoma and height trended in men
- **Conclusion:**
  - After adjusting for sun exposure, tall stature may be risk factor for skin cancer

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**Key issues in Melanoma**

**Prevention:**

*UV Protection*

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**Does Sunscreen Usage Lower Skin Cancer Risk?**
Reduced melanoma risk after regular sunscreen use

- 1,621 randomly selected residents of Nambour (Queensland) Australia, age 25 to 75 years, were randomly assigned to daily or discretionary sunscreen application to head and arms
- Treated for 5 years then followed for 10 years

Green et al, J Clin Oncol, 2011

Sunscreen Usage and Melanoma Risk

- Invasive MM:
  - Discretionary: 0.27
  - Daily: 1.0

- All Melanomas:
  - Discretionary: 0.5
  - Daily: 1.0

Green et al, J Clin Oncol, 2011

Skin cancers in Australia prevented by regular sunscreen use

- Estimated the proportion of skin cancers that would have occurred but were likely prevented by regular sunscreen use
- Regular sunscreen use prevented around 14,190 persons from developing SCCs (PF 9.3%) and 1,730 from Melanoma (PF 14%)
- Conclusions:
  - Prevailing levels of sunscreen use probably reduced skin cancer incidence by 10-15%
  - Sunscreen should be a component of a comprehensive sun protection strategy


MM risk using SPF<15 vs SPF >15

Norwegian Women Study N = 143,844

Ghiasvand et al, J Clin Oncol, 2016
How high is high enough?

Does SPF>50 provide additional benefit?

In-vivo comparison of SPF 100 vs 50 in Actual Use Conditions

**METHODS**

- 199 healthy men and women ≥18 years of age participated in a one day split face, randomized, double blind study in Vail, Colorado.
- The difference in sunburn protection provided by two currently available sunscreens (SPF 50+ and SPF 100+) was evaluated.
- Products were supplied in a kit containing two overwrapped tubes of sunscreen marked “right” and “left.” Each subject wore both sunscreens simultaneously, with product application randomized to either the right or left side of the face.
- Subjects utilized the sunscreens as they would normally during ski activities. Diaries were used to record sun exposure time and the frequency and timing of sunscreen re-applications.
- Subjects reported the next morning for clinical evaluation.

**RESULTS**

**Primary Endpoint**

SPF 100+ sunscreen was significantly more effective at protecting against sunburn than was SPF 50+ sunscreen

**RESULTS**

**Usage**

No differences were observed in usage, application density, or reapplication frequency of the study products

![Graph showing results](image)
RESULTS
Secondary Endpoint
Erythema was significantly lower on the SPF 100+ protected side of the face, and erythema progression was observed to be more than twice as severe on the SPF 50+ protected side.

RESULTS
Post Hoc Analysis
The number of sunscreen reapplications was not observed to diminish the enhanced protection benefit of the SPF 100+ product.

RESULTS
Post Hoc Analysis
SPF 100+ sunscreen was significantly more effective at protecting against sunburn in all examined skin types.

CONCLUSIONS
• The SPF 100+ sunscreen was significantly more effective in protecting against sunburn than the SPF 50+ sunscreen for all skin types evaluated.
• These findings demonstrate that there is a need for sunscreens labelled with SPF5 greater than 50+ to provide consumers with better choices for sunburn protection.

Key issues in Melanoma
Management

Goals of Wide Excision in Cutaneous Melanoma
To completely excise all melanoma cells while minimizing morbidity, cosmetic disfigurement, functional impairment, and cost.
Melanoma Excision Margins
How wide is wide enough?

How narrow is too narrow?

Melanoma Surgical Margins
Current Recommendations

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Margins</th>
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<tbody>
<tr>
<td>In-situ</td>
<td>5 millimeters</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>1 centimeter</td>
</tr>
<tr>
<td>1 – 2 mm</td>
<td>1 – 2 centimeters</td>
</tr>
<tr>
<td>&gt;2 mm</td>
<td>2 centimeters</td>
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</tbody>
</table>

Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: randomized trial survival analysis

- Previously published randomized trial (same researchers) of narrow (1 cm) versus wide (3 cm) excision margins in pts with thick cutaneous MMs showed narrow margins were associated with an increased frequency of locoregional relapse
- Current guidelines advise a 2 cm margin for MMs >2 mm in thickness
- Multicenter trial at 59 hospitals
- 900 pts with one primary localized MM greater than 2 mm in Breslow thickness on the trunk or limbs (excluding palms or soles) were randomly assigned (1:1) to receive surgery with either a 1 cm or 3 cm excision margin following an initial surgery

Hayes et al, Lancet Oncol, 2016

Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: randomized trial survival analysis

Overall survival

MM-specific survival

Hayes et al, Lancet Oncol, 2016
**Conclusions:**
- A 1 cm excision margin may be **INADEQUATE** for cutaneous melanoma with Breslow thickness greater than 2 mm on the trunk and limbs.
- Adequacy of a 1 cm margin for thinner melanomas with poor prognostic features should be addressed in future randomized studies.

**Management of MM by US Dermatologists**
- Email survey of US Dermatologists (n=510, 8% response rate) performed in August 2015
- Asked questions on how they evaluated and managed MM
- Conclusions:
  - Guidelines only partially followed
  - Large differences in approaches
  - Differences in approaches by experience
  - Educational opportunity exists
  - Maybe guidelines may be need to be reviewed/revised

**Risk of subsequent melanoma after MMIS and invasive MM**
- From 1973 to 2011, 55,661 MMIS and 112,613 with invasive MM as their first primary cancer of any type and as their first primary cancer.
- 5817 individuals (3.5%) developed at least 1 subsequent melanoma in situ. Incidence rate of subsequent melanoma in situ was 3.8 per 1000 person-years.
- 6067 individuals (3.6%) developed at least 1 subsequent invasive melanoma. Incidence rate of subsequent invasive melanoma was 3.7 per 1000 person-years.
- Is that higher than the general population?
Risk of Developing MM

- Annual incidence per 100K
- 15X increased risk

Risk of subsequent melanoma after MMIS and invasive MM

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- 5817 individuals (3.5%) developed at least 1 subsequent melanoma in situ. Incidence rate of subsequent melanoma in situ was 3.8 per 1000 person-years,
- 6067 individuals (3.6%) developed at least 1 subsequent invasive melanoma. Incidence rate of subsequent invasive melanoma was 3.7 per 1000 person-years
- Cumulative lifetime risk for subsequent melanoma approached 20%

Conclusions:
- Melanoma patients need to be followed closely for:
  - Risk of spread of disease from their initial tumors
  - Risk of development of additional primary melanomas

Follow Up Dx &lt;5yrs

- q3month: 25%
- q6month: 49%
- q12month: 2%
- other: 24%

Follow Up Dx &gt;5yrs

- q3month: 2%
- q6month: 30%
- q12month: 63%
- other: 5%
Key issues in Melanoma

Diagnosis

<table>
<thead>
<tr>
<th>Device</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MelaFind</td>
<td>95-100%</td>
<td>75-89%</td>
<td>Multispectral sequence of images created in 3 seconds</td>
</tr>
<tr>
<td>Molemax</td>
<td>-</td>
<td>-</td>
<td>Total body photography. No computer diagnostic analysis</td>
</tr>
<tr>
<td>SIAscope</td>
<td>83-96%</td>
<td>85-87%</td>
<td>Diagnosis of lesions as small as 2 mm in diameter</td>
</tr>
<tr>
<td>SolarScan</td>
<td>91%</td>
<td>68%</td>
<td>Empirical database for comparison; recorded on graphic map of body</td>
</tr>
<tr>
<td>Confocal Laser Microscopy</td>
<td>98%</td>
<td>98%</td>
<td>Histopathological evaluation at testable with similar criteria; longer wavelengths can measure into papillary dermis</td>
</tr>
</tbody>
</table>

Melanoma 10 Year Survival

Pollack et al, J Amer Acad Dermatol, 2011

<table>
<thead>
<tr>
<th>Stage</th>
<th>% Surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>92%</td>
</tr>
<tr>
<td>Regional</td>
<td>54%</td>
</tr>
<tr>
<td>Distant</td>
<td>12%</td>
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Melanoma Diagnostic Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optical Coherence Tomography (OCT)</td>
<td>-</td>
<td>-</td>
<td>High resolution cross-sectional images resembling histopathological section of skin; higher resolution than ultrasound and greater detection depth than CSLM</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>99%</td>
<td>99%</td>
<td>Tumor thickness may be overestimated because of underlying inflammatory infiltrate</td>
</tr>
<tr>
<td>Tape Stripping mRNA</td>
<td>69%</td>
<td>79%</td>
<td>Practical for any skin surface; can retest same lesion</td>
</tr>
<tr>
<td>Electrical Biimpedance</td>
<td>92-100%</td>
<td>67-80%</td>
<td>Electrical impedance properties of human skin vary significantly with the body location, age, gender, and season</td>
</tr>
</tbody>
</table>

Prognosis

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Disease-Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN status</td>
<td>HR: 6.53, 95% CI: 6.39 – 12.58, P &lt; .0001</td>
</tr>
<tr>
<td>Tumor thickness</td>
<td>HR: 1.23, 95% CI: 1.10 – 1.38, P &lt; .0001</td>
</tr>
<tr>
<td>Clark level II</td>
<td>HR: 2.32, 95% CI: 1.03 – 5.23, P &lt; .01</td>
</tr>
<tr>
<td>Ulceration</td>
<td>HR: 1.62, 95% CI: 0.85 – 3.08, P &lt; .05</td>
</tr>
<tr>
<td>Axial location</td>
<td>HR: 1.72, 95% CI: 0.85 – 3.45, P &lt; .05</td>
</tr>
<tr>
<td>Age</td>
<td>HR: 1.01, 95% CI: 0.98 – 1.01, P &lt; .1</td>
</tr>
<tr>
<td>Sex</td>
<td>HR: 1.11, 95% CI: 0.45 – 1.82, P &lt; .1</td>
</tr>
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HR = Hazard ratio
CI = Confidence interval

Key issues in Melanoma

Genetics
Diagnosis
Prognosis
Therapy

Can we use genetics to diagnose melanoma?

What does the 23 genetic expression profile (23-GEP) test do?

- Premise: Benign and malignant melanocytic lesions behave differently (invasion, metastasis, immune function etc.) and this is associated with expression of different (and/or different amounts of) RNAs.
- Identified a panel of 23 genes that are differentially expressed in benign and malignant melanocytic lesions and has developed a myPath test that
  - purifies RNA from the tissue
  - quantifies how much of each of the 23 RNAs is expressed
  - applies a mathematical algorithm to objectively determine if the lesion is benign or malignant based on the expression pattern

What does the 23 genetic expression profile (23-GEP) test do?

Benign

???

Melanoma

Clinically or Histologically Unsure Pigmented Lesion

Can we use genetics to identify a subset of melanoma patients at higher risk for developing metastatic disease?

Invasive MM US Cases by Thickness
SEER 1992-2003

Landow et al, SID poster, 2016
More people die from thin melanomas than thick melanomas

- 4,218 Australians who died from melanoma between 1990 and 2009, thin melanomas (<1mm) accounted for 23% of melanoma deaths overall
- More people died from thin melanomas (296 deaths, 23%) than from thick melanomas more than 4 mm in thickness (186 deaths, 14%) or from metastatic presentations (207 deaths, 16%).
- Conclusions:
  - More people with thin melanomas die than with thick melanomas because there are so many more thin lesions

Clinical Issue in Early Stage Melanoma

- All newer therapies and regional interventions are effective in metastatic melanoma
- Within Stage IV use and resected Stage III disease, early intervention is consistently shown to be a (or in many cases the most) significant predictor of response
- While AJCC clinicopathologic factors are good, it is the majority of deaths occur in early stage disease
- Prognostic accuracy needs to be improved as it has direct implications on how we follow up our patients

Pathology Review of Thin MM and MMIS

- Overall pathologic discordance rate in diagnosis 4% (15/420 pts)
- Overall change in tumor staging rate 24% (97/405 pts)
- Changes in surgical excision margins in 12% of pts (52/420 pts)
- Decision about performing a sentinel lymph node biopsy in 16% of pts (67/420 pts)
- Conclusions:
  - Review of thin MM or MMIS by an expert dermatopathologist results in frequent, clinically meaningful alterations in diagnosis, staging, prognosis, and surgical treatment

Detection of Occult Invasion in Melanoma In Situ

- Unequivocal MMIS without associated nevi or regression was identified using a consecutive sample of 33 cases
- 3 sequential slides were stained with H&E and melan-A.
- Melan-A stained slides showing definitive invasion were double-stained with Sry-related HMG-Box gene 10 (SOX10) to confirm the melanocytic nature of the cells
- Occult invasive melanoma was detected in 11 of 33 consecutive cases (33%) of previously diagnosed MMIS
- 6 of 11 melanomas (55%) were diagnosable only by immunohistochemistry
- Conclusions:
  - History and physical examination including regional lymph nodes, education, and surveillance recommendations should be based on a very low, but not zero, risk of metastasis for MMIS

**What if we could non-invasively identify patients who will have aggressive disease?**
**What is the Melanoma Gene Expression Profile Test (31-GEP)**

- Identifies a genomic profile, not genetic mutations
- Validated proprietary 31-gene expression profile test
- Uses in formalin-fixed, paraffin-embedded tissue specimen obtained from primary biopsy
  - That is, no special processing on behalf of the dermatologist or dermatopathologist

**GEP Test Workflow**

1. **Primary melanoma tumor tissue**
2. RNA isolation
3. cDNA generation and amplification (14X)
4. Microfluidics PCR gene card
   - 28 discriminant gene targets and 3 control genes
5. Analysis of GEP with a proprietary algorithm to determine class and metastatic risk
   - Class 1: low metastatic risk
   - Class 2: high metastatic risk

**GEP-31 Kaplan Meir Survival Curves**

- **Uveal Melanoma**
  - Class 1: Low Risk of metastasis within 5 years
  - Class 2: High Risk of metastasis within 5 years

- **Cutaneous Melanoma**
  - Low Risk of metastasis within 5 years
  - High Risk of metastasis within 5 years

**3 validation studies of 31-GEP test**

- Black: Integrate and Expand (p=4.4 e-08)
- Green: Zitelli & Brodland (p=1.4 e-06)
- Violet: Castle 574 (p=2.6 e-16)
Can the 31-GEP Test Use Melanoma Tumor Biology to Improve Risk Prediction Based on Clinical Factors?

- AJCC online tool: melanomaprognosis.org
  - Using AJCC database, estimates an individual patient risk using additional clinical factors
  - Study compared results from online tool risk prediction to DecisionDx-Melanoma class determination
  - 205 Stage I and II patients from ongoing DecisionDx-Melanoma validation cohort had all criteria for web prediction tool

Ferris et al. Abstract #2050, American Academy of Dermatology, March 2015

Deaths

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<tr>
<td>High risk</td>
<td>50</td>
</tr>
<tr>
<td>Low risk</td>
<td>20</td>
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AJCC Online—Alone

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<tr>
<td>AJCC low risk</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>AJCC high risk</td>
<td>30 (60%)</td>
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High risk by GEP or AJCC Online

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<tbody>
<tr>
<td>Low risk</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>High risk</td>
<td>41 (82%)</td>
</tr>
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</table>

Cox Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant metastasis</td>
<td>1.9</td>
<td>1.0-4.4</td>
<td>0.05</td>
</tr>
<tr>
<td>AJCC Class 79%</td>
<td>1.7</td>
<td>0.5-5.9</td>
<td>0.3</td>
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Using 31-GEP with AJCC On-line Tool Improves Prognostic Accuracy

31-GEP Test Melanoma Analysis with SLNBx Status

- This analysis shows that both SLNB positive status and 31-GEP Melanoma Class 2 are important predictors of DMFS and OS.
- SLNB identified ~30% of patients who died, but 70% of patients who died were SLNB negative.
- Performing the 31-GEP Melanoma assay in the SLNB negative cohort identified over 80% of those SLNB negative patients who developed distant metastasis and died.

31-GEP in SLNB- Patients

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<tbody>
<tr>
<td>DMFS</td>
<td>1086420</td>
</tr>
<tr>
<td>p &lt; 0.0001</td>
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Case Study Presentation

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<table>
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<tr>
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<tbody>
<tr>
<td>Patient A</td>
<td>Patient B</td>
</tr>
<tr>
<td>Age</td>
<td>59</td>
</tr>
<tr>
<td>Lesion site</td>
<td>Extremity</td>
</tr>
<tr>
<td>Tumor thickness</td>
<td>1.35</td>
</tr>
<tr>
<td>Ulceration</td>
<td>No</td>
</tr>
<tr>
<td>Stage</td>
<td>III</td>
</tr>
<tr>
<td>SLN Status</td>
<td>Negative</td>
</tr>
<tr>
<td>AJCC 5-year survival estimate</td>
<td>66.7%</td>
</tr>
</tbody>
</table>

DecisionDx-Melanoma Test Result. 5-year estimates:

Class 1 result: 97% chance of metastasis-free
Class 2 result: 31% chance of metastasis-free

Clinical Outcome: Metastasis-free at 10 years post-diagnosis
Metastasized at 0.6 year post-diagnosis (lung)

Case Study Presentation

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patient X</td>
<td>Patient Y</td>
</tr>
<tr>
<td>Age</td>
<td>70</td>
</tr>
<tr>
<td>Lesion site</td>
<td>Extremity</td>
</tr>
<tr>
<td>Tumor thickness</td>
<td>3.5</td>
</tr>
<tr>
<td>Ulceration</td>
<td>No</td>
</tr>
<tr>
<td>Stage</td>
<td>IIA</td>
</tr>
<tr>
<td>SLN Status</td>
<td>Negative</td>
</tr>
<tr>
<td>AJCC 5-year survival estimate</td>
<td>73.5%</td>
</tr>
</tbody>
</table>

DecisionDx-Melanoma Test Result. 5-year estimates:

Class 1 result: 97% chance of metastasis-free
Class 2 result: 31% chance of metastasis-free

Clinical Outcome: Metastasis-free at 4.4 years post-diagnosis
Metastasized at 2 year post-diagnosis (lung)
Impact of a test on management

Would you do a SLNBx?

A 69-year old male with a 0.76 mm, ulcerated melanoma of the mid-chest underwent wide local excision

Would you pursue imaging?

A 69-year old male with a 0.76 mm, ulcerated melanoma of the mid-chest underwent wide local excision

Key issues in Melanoma

Advanced Disease

Targeted Therapy for Melanoma

2010

The end...
Targeting Approaches to Systemic MM

- **BRAF inhibitors**
  - Interrupts the B-Raf/MEK step on the activation pathway – if the B-Raf has the V600E mutation

- **MEK inhibitors**
  - Inhibits the mitogen-activated protein kinase enzymes MEK1 and/or MEK2

- **PD-1 blockers**
  - Programmed death 1 (PD-1) receptor is a negative regulator of T-cell effector mechanisms that limits immune responses against cancer

- **CTLA-4 antibodies**
  - CTLA-4 inhibits T cell responses

BRAF Biology

<table>
<thead>
<tr>
<th>Normal amino acid sequence</th>
<th>V600E mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu</td>
<td>Val</td>
</tr>
</tbody>
</table>

BRAF → MAP Kinase

Locks BRAF into the active signaling position so it continuously drives MAP kinase pathway independent of other inputs

The MM being considered for Treatment with a BRAF inhibitor must have the BRAF mutation

MM tissue from the path block is sent for testing
Progression-free Survival

Flaherty et al. NEJM 363:809-19, 2010

(MM survival in BRAF V600 mutant MM treated with Vemurafenib

Sosman et al., NEJM, 2012

The BRAF inhibitor paradox — BRAF inhibitors inhibit the MAPK pathway in BRAF mutant cells but activate the pathway in cells driven by the MAPK pathway other than through oncogenic BRAF mutation.

Sullivan et al., Eur J Cancer, 2013
**Overview Photography and Short-term Mole Monitoring in Patients Taking a BRAF Inhibitor**

- 22 MM pts on BRAF inhibitors followed for 11 months looking at PSL change and MM development
- 42 new or changing PSLs (7 were new MMs)
- New MM incidence was 43,500/100,000 person-years of BRAF inhibitor therapy (US incidence is 25/100,000)
- 1740x increased incidence

**Conclusions:**
- Total body photography and mole monitoring with dermoscopy effective in monitoring atypical PSLs in the highly volatile melanocytic changes in patients taking a BRAF inhibitor

*Yagerman et al, JAMA Dermatol, 2014*

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**Nivolumab Therapy for Advanced MM**

- Nivolumab is a fully human IgG4 antibody that blocks the programmed death 1 (PD-1) receptor
- 94 pts with advanced melanoma received anti–PD-1 antibody at a dose of 0.1 to 10.0 mg per kilogram of body weight every 2 weeks
- Pts received up to 12 cycles until disease progression or a complete response occurred. Response was assessed after each 8-week treatment cycle.
- Response rate of 28% (26 of 94 pts). 20 lasted > 1 year
- Drug-related serious adverse events occurred in 11% including pneumonitis, vitiligo, hepatitis, hypophysitis, and thyroiditis


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**Activity of Anti–Programmed Death 1 (PD-1) Antibody in Patients with Treatment-Refractory MM**


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**Expanded Indications for Nivolumab**

- Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with:
  - BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
  - BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.
  - Unresectable or metastatic melanoma, in combination with ipilimumab.
**Cutaneous adverse events of anti-programmed cell death (PD)-1 therapy in patients with metastatic MM**

N=82  49% developed a form of anti-PD-1-associated cutaneous adverse events

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**Potential Advantage of Combination Therapy**

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**Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations**

**Clinical Activity in Patients Receiving Concurrent Regimen of Nivolumab and Ipilimumab**

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**Targeted Therapies for Melanoma Pathways**

<table>
<thead>
<tr>
<th>BRAF</th>
<th>MEK</th>
<th>CTLA-4</th>
<th>PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>Trametinib</td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Cobimetinib</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
</tr>
</tbody>
</table>
If 2 are good, are 3 better?

Pathway 1
Pathway 2
Pathway 3

Targeted Melanoma Blockade
Pembrolizumab in Combination With Dabrafenib and Trametinib

Maximum Percentage Change From Baseline in Tumor Size
Longitudinal Change From Baseline in Tumor Size


Vem + Cobimetinib + Atezo
Reduction in Tumor Burden

Key issues in Melanoma
Predicting response to treatment

Phase III Trial of IPI + NIVO vs IPI vs NIVO: Predicting treatment response

Association of a Neoeptope Signature with a Clinical Benefit from CTLA-4 Blockade

ORR, % (95% CI)

Higher LDH has a lower response rate

NIVO+IPI  NIVO  IPI

Phase III Trial of IPI + NIVO vs IPI vs NIVO:
Predicting treatment response

Association of a Neoeptope Signature with a Clinical Benefit from CTLA-4 Blockade
Association of a Neoepitope Signature with a Clinical Benefit from CTLA-4 Blockade

- Tumor specimens from 42 patients were analyzed for PD-L1 expression on the surface of tumor cells.
- Biopsy specimens from 25 of the 42 pts were positive for PD-L1 expression by immunohistochemical analysis.
- 9/25 PD-L1(36%) had an objective response vs. 0/17 patients with PD-L1–negative tumors had an objective response.

Nivolumab Therapy for Advanced MM

- Key issues in Melanoma
  - Is there now a cure for melanoma?

- PD-1 Molecular Marker Assessments in Nivolumab Treated Pts

- CTLA-4/PD-1/CD8+ T Cells as a Predictive Biomarker for Outcome With Pembrolizumab

- Nivolumab Phase Ib Follow-up:
  - Overall Survival at Plateaus at 3 Years
Melanoma

The future

Epidemiology
Risk Factors
Prevention
Management
Genetics
- Diagnosis
- Prognosis
- Advanced disease therapy