Melanoma Update 2018

Key issues you need to know

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY
Darrell S, Rigel, MD
Melanoma Update – 2018
Key issues you need to know

Castle – A, H, I
Neutrogena-S,H

Key issues in Melanoma

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

Epidemiology:

Incidence and Mortality

Cancer USA - 2018

Skin Cancer USA - 2018

More Skin Cancers than all other cancers combined
Melanoma – US 2018

- Invasive = 91,270
- In-situ = 87,290

Leading Sites of New Cancer Cases – 2018 Estimates

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<tr>
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<th>Male</th>
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<td>75+</td>
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Melanoma – USA 2018

- 178,560 total cases

- Males
- Females

Annual % Incidence Change


Holman et al., JAMA Dermatol, 2018

US Annual Deaths from Melanoma

ACS

Skin Cancer Deaths US - 2018

Who gets Melanoma?

Over 1 American dies of Melanoma every hour

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

Maiorino A et al, J Dermatolog Treat, 2016

Post-diagnosis aspirin use and overall survival in MM pts

- 1522 MM pts had ASA use evaluated
- Aspirin use was associated with longer overall survival
- Not associated with survival in patients with in situ and stage I melanoma, but was associated with better survival in stages II (HR 0.45) and III (HR 0.57)
- Pts using aspirin before diagnosis were less likely to be diagnosed with stage III or IV disease
- Conclusions:
  - Aspirin could provide a survival advantage in melanoma.
  - Clinical trials 37 investigating the therapeutic potential of aspirin are warranted.

Rachidi et al. JAAD, 2017
**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


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**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:
  - PDE5-1 use associated with increased risk of MM & BCC

Loeb S et al. JAMA. 2015

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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

Li et al, JAMA Internal Medicine, 2015

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**Phosphodiesterase type 5 (PDE5) inhibitors and MM risk**

- Meta-analysis
- 5 observational studies reviewed
- PDE5 use was slightly but significantly associated with increased MM risk (OR=1.12).
- Conclusions:
  - PDE5 usage directly correlated with MM development but at a low level.
  - Well conducted prospective studies needed to confirm association

Tang et al, JAMA. 2017

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**Key issues in Melanoma**

**Prevention:**

**UV Protection**
If current trends continue, sprays will soon overtake lotions as the primary sunscreen formulation.

Given this fact, dermatologists and manufacturers need to work together to establish guidelines for optimal application and usage of spray sunscreens to achieve the maximal skin cancer prevention benefit.

Does Sunscreen Usage Lower Melanoma 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

Sunscreen Usage and Melanoma Risk

- All Melanomas
- Invasive MMs

Relative Risk

- Discretionary
- Daily
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
• Only 11 new MMs in daily group vs. 22 (p=0.051)
• 2 Invasive MMs in daily group vs.11
• Conclusions:
  – Melanoma may be preventable by regular sunscreen use in adults

Green et al, J Clin Oncol, 2011

How many melanomas might be prevented if more people applied sunscreen regularly?

Calculated the PF, the proportional difference between the observed number of melanomas arising under prevailing levels of 5% annual increase in sunscreen use for 10 years (50% increase)

Estimated that cumulatively to 2031, 231,053 fewer melanomas would arise in the U.S. white population (PF 11%)

Olsen et al, Br J Dermatol, 2017

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Conclusions:
• Interventions to increase use of sunscreen would result in reductions in melanoma incidence
• Countries with a high incidence of melanoma should monitor levels of sunscreen use

Olsen et al, Br J Dermatol, 2017

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Olsen et al, Br J Dermatol, 2017
How high is high enough?

High SPF formulation more effective during intense UV exposures

- SPF 85 formulation tested vs. SPF 50
- 56 subjects applied sunscreen to face while skiing at Vail, Colorado 1/13/08
- 1 application only at start of day
- Average hours exposed 5.0 hours
- Noon Sun 22 minutes = 1 MED
- 7/28 sunburned SPF 50 vs. 1/28 SPF 85 (p=0.02)

Conclusion:
- SPF 85 formulation more effective than SPF 50 in protecting from sunburn with a single application in a high UV test environment

Russak et al, JAAD 2010

Does SPF>50 provide additional benefit?

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.

Williams et al, JAAD, 2018

RESULTS Primary Endpoint

SPF 50 side of face 11x more likely to be sunburned than SPF 100 side

Williams et al, JAAD, 2018
Erythema progression was observed to be more than twice as severe on the SPF 50 vs SPF 100 protected side.

RESULTS

Usage

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

The number of sunscreen reapplications was not observed to diminish the enhanced protection benefit of the SPF 100 product.

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 SPF>50+ to provide consumers with better choices for sunburn protection.
Diagnosis

1985

For Early Melanoma... Remember Your ABCD's!

- A = Asymmetry
- B = Border irregular
- C = Color uneven
- D = Diameter > 1/4"
- E = Evolving

JAMA, 2004

ABCD Rule for MM Diagnosis

- ABCD rule improved diagnostic skills
- Sensitivity and specificity improved
- Conclusion:
  - Level of Diagnosis improved for dermatologists and non-dermatologists

Whited et al, JAMA, 1998

Melanoma US 10 Year Survival

92% 54% 12%
- Localized  Regional  Distant

Pollack et al, J Amer Acad Dermatol, 2011

Using Technology to Enhance Early Detection
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

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

<table>
<thead>
<tr>
<th>Invasive MM US Cases by Thickness</th>
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</thead>
<tbody>
<tr>
<td>SEER 1992-2003</td>
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<tr>
<td>&lt;1mm</td>
</tr>
<tr>
<td>1-1.99mm</td>
</tr>
<tr>
<td>2-3.99mm</td>
</tr>
<tr>
<td>4+mm</td>
</tr>
<tr>
<td>72%</td>
</tr>
<tr>
<td>16%</td>
</tr>
<tr>
<td>8%</td>
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<tr>
<td>4%</td>
</tr>
</tbody>
</table>

Landow et al, SID poster, 2016
Invasive MM US Deaths by Thickness
SEER 1992-2003

- 29% <1mm
- 27% 1-1.99mm
- 17% 2-3.99mm
- 27% 4+mm

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

Whiteman and Olsen, WCCS 2014

Pathology Review of Thin MM and MMIS
Impact on Treatment Decisions

- 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

Santillan et al, J Clin Oncol, 2010

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

Bax et al. JAMA Dermatol, 2016

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

Bax et al. JAMA Dermatol, 2016

GEP Test Workflow

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

- Uses formalin-fixed, paraffin-embedded tissue
- Quantifies expression of 31 genes from primary tumor
- Applies a validation algorithm
- Classifies patients as low vs. high risk

Class 1 test result:
Low Risk of metastasis within 5 years

Class 2 test result:
High risk of metastasis within 5 years

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.

If SLNBx is Negative, 31-GEP Status is Predictive of Prognosis

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

**Impact of surgical timing on survival in cutaneous melanoma**

- 153,218 patients with stage I-III melanoma in the National Cancer Database were assessed.
- On multivariate analysis stratified by stage, increased time from biopsy to surgery increased mortality risk in stage I pts relative to those treated within 30 days:
  - <30 days (HR 1.05, 95% CI 1.01, 1.1)
  - 30-59 days (HR 1.16, 95% CI 1.07, 1.25)
  - 60-89 days (HR 1.29, 95% CI 1.12, 1.48)
  - >90 days (HR 1.41, 95% CI 1.21, 1.65)
- Conclusions:
  - Surgical timing did not significantly impact survival in stage II/III disease.
  - Definitive treatment of stage I melanoma within 30 days improves patient survival.

**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?

Melanoma Surgical Margins
Current Recommendations

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<th>Thickness</th>
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<tr>
<td>&gt;2 mm</td>
<td>2 centimeters</td>
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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
Conclusions:
- 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 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 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

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**Should SLNBx be performed?**

**NCCN SLNBx recommendations (2018):**

- 0-5% SLNB+ rate = do not perform
- 5-10% SLNB+ rate = discuss and consider
- ≥10% SLNB+ rate = discuss and offer

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**Mitotic rate is associated with positive SLN in thin MMs**

- 17,204 melanomas with Breslow depth 0.01 to 1.0 mm retrospectively examined
- Melanomas in patients with SLNB+ had significantly higher mitotic rate than in those with SLNB- (3.46 vs 1.54, p<0.0001)
- Multivariate analysis adjusting for age, gender, race, Breslow depth, and ulceration showed that patients with mitotic rate >1 were more than 2x as likely to be SLN-positive (OR 2.13)

**Conclusions:**
- Mitotic rate appears to be strongly associated with lymph node positivity in thin melanomas (Breslow depth 0.01-1.0 mm)
- Despite upcoming changes in AJCC guidelines, this information has value and should be continued to be documented on pathology reports
ASCO guidelines update on SLNBx and management of regional LNs in MM

• Guidelines updated based on interval publication of:
  – 9 observational studies
  – 2 systematic reviews
  – 2 updated randomized, controlled trials
    • Multicenter Selective Lymphadenectomy II (MSLT-II)
    • German Dermatologic Oncology Cooperative Group (DeCOG-SLT)

• Sought to address 2 key questions:
  – What are the indications for SLNBx?
  – What is the role of completion lymph node dissection?

Wong et al. J Clin Oncology, 2018

Completion Dissection or Observation for SLN Metastasis in MM

• Randomly assigned patients with SLN mets detected by means of standard pathological assessment or a multimarker molecular assay to immediate completion lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group).

• Primary end point was melanoma-specific survival

• Immediate completion lymph-node dissection was not associated with increased MM-specific survival

• Disease-free survival was slightly higher in the dissection group than in the observation group

• Lymphedema was observed in 24% of the patients in the dissection group vs. 6% of those in the observation group

Faries et al. NEJM, 2017

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• Disease-free survival was slightly higher in the dissection group than in the observation group

• Lymphedema was observed in 24% of the patients in the dissection group vs. 6% of those in the observation group

• Conclusions:
  – Immediate completion LN dissection increased rate of regional disease control and provided prognostic information but did not increase MM-specific survival among pts with MM and SN mets.

Faries et al. NEJM, 2017

ASCO guideline update on SLNBx and management of regional LNs in MM

Key Recommendations

• Thin MMs:
  – Routine SLNBx is not recommended for patients with MMs that are T1a (non-ulcerated lesions < 0.8mm in thickness)
  – SLNBx may be considered for T1b pts (0.8 to 1.0mm or < 0.8mm with ulceration) after a thorough discussion with pt of potential benefits and risks of procedure-associated harm

• Intermediate thickness MMs:
  – SLNBx is recommended for patients with MMs that are T2 or T3 (1.0 to 4.0mm)

• Thick MMs:
  – SLN biopsy may be recommended for patients with MMs that are T4 (> 4.0mm), after a thorough discussion with pt of potential benefits and risks of procedure-associated harm

Wong et al. J Clin Oncology, 2018
ASCO guideline update on SLNBx and management of regional LNs in MM
Key Recommendations for Completion Dissection

- Either CLND or careful observation may be offered to patients with low risk micrometastatic disease, with due consideration of clinicopathological factors.
- For higher risk patients, careful observation may be offered only after a thorough discussion with patients about the potential risks and benefits of NOT performing CLND.

Wong et al. J Clin Oncology, 2018

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31-GEP - Cox regression analysis for cases with thin (≤1mm) tumors and SLNBx performed shows strong prognostic value in this population

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<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p value</td>
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<tr>
<td>Breslow depth</td>
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<td>0.01-15.9</td>
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<td>5.4</td>
<td>1.2-23.3</td>
<td>0.03</td>
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*Not factors significant in multivariate models for DMFS or MSS

Cook et al. IPCC Meeting 2017

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Can 31-GEP guide SLNB patient selection?

- Currently, SLNB is necessary in order to consider a patient as a Stage III and eligible for adjuvant therapy interventions.
- However, it is estimated that the rate of SLN positivity is 16% in the general population, which means 84% of patients do not benefit from this procedure.
- Older age is associated with a poor prognosis, yet fewer elderly patients are SLN positive.
- Likewise, a negative SLNB in head and neck melanoma is known to have higher recurrence rates than a negative SLNB in trunk or extremity melanomas.
- There is an association between 31-GEP Class 1 and lower rates of positive SLNB results.
- Could 31-GEP identify a population with ≤5% positive rate for SLNB?


Can 31-GEP be used to increased the yield of SLNBx?

NCCN SLNBx recommendations (1/18):

0-5% SLNB+ rate = do not perform
5-10% SLNB+ rate = discuss and consider
≥10% SLNB+ rate = discuss and offer

Impact on SLNBx Procedures reduced by 52%

---

What happens to a T1/T2 patient?

Patient with T1/T2 Melanoma

- Decision: Melanoma

Class 1: No SLNB
- MSS: 96.2%
- O1: 97.2%
- DMFS: 83.6%
- RFS: 95.7%

Class 2: SLNB
- MSS: 95.3%
- O1: 95.3%
- DMFS: 86.3%
- RFS: 77.2%

NCCN SLNBx recommendations (1/18):

- ConfirmMDx: Prostate cancer
  - Rule-out repeat biopsies after negative prostate biopsy: 90%
- Percepta: Lung cancer
  - Rule-out invasive procedures after bronchoscopy: 91%
- Affirma: Thyroid cancer
  - Rule-out surgery for indeterminate thyroid nodules: 94%
- Thyramir: Thyroid cancer
  - Rule-out surgery for indeterminate thyroid nodules: 94%
- Melanoma 31-GEP: Cutaneous melanoma
  - Rule-out SLNB biopsy in cutaneous melanoma: 96%

Melanoma 31-GEP’s NPV supports guidance of SLNBx

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
<th>Endpoint</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ConfirmMDx</td>
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</table>

*In an older patients
Managing Advanced Disease

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


Melanoma in Pregnancy

- There is controversy in the literature as to whether pregnancy-associated melanoma has worse survival than other melanomas.
- Any changing-pigmented lesion should be biopsied, regardless of pregnancy hyperpigmentation.
- Increased lymphangiogenesis in pregnancy is associated with increased metastasis - timely diagnosis is therefore imperative.
- It is generally accepted that oral contraceptive use in not absolutely contraindicated after a diagnosis of melanoma in pregnancy.

Still et al, Obstet Med, 2017

Hazard rates for recurrence in Melanoma

- Hazard rates are what is the chance of Melanoma clinically recurring at a given point in time
- For Melanoma, if there is clinically recurrent disease, it will occur:
  - 90% of the time in 2 years
  - 95% of the time in 5 years
  - 99% of the time in 10 years
- Higher risk for earlier recurrence for more advanced disease

Melanoma in Pregnancy

- There is controversy in the literature as to whether pregnancy-associated melanoma has worse survival than other melanomas.
- Any changing-pigmented lesion should be biopsied, regardless of pregnancy hyperpigmentation.
- Increased lymphangiogenesis in pregnancy is associated with increased metastasis - timely diagnosis is therefore imperative.
- It is generally accepted that oral contraceptive use in not absolutely contraindicated after a diagnosis of melanoma in pregnancy.

Conclusions:
- Subsequent pregnancy should be delayed for two to three years after a diagnosis of melanoma with a high risk of recurrence

Still et al, Obstet Med, 2017

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

Normal amino acid sequence

V600E mutation

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

cobas® 4800 BRAF V600 Mutation Test detects the BRAF V600E mutation in formalin-fixed, paraffin-embedded human melanoma tissue

Test has 97.3% positive agreement in detecting the BRAF V600E (1799 T>A) mutation

Vemurafenib

• 675 previously untreated MM pts with the BRAF V600E mutation.
• Phase 3 randomized clinical trial
• Comparing vemurafenib with dacarbazine with previously untreated, metastatic melanoma
• At 6 months, overall survival was 84% in the vemurafenib group vs. 64% in dacarbazine group.
• Conclusion:
  − Vemurafenib produced improved survival rates in patients with previously untreated melanoma with the BRAF V600E mutation.

Overall Survival

Chapman et al, NEJM, 2010

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

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.

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

Targeting Approaches to Systemic MM

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Improved survival with MEK inhibition by trametinib in BRAF-mutated melanoma

- Median progression-free survival was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (hazard ratio for disease progression or death in the trametinib group, 0.45; 95% confidence interval [CI], 0.33 to 0.63; P<0.001).
- At 6 months, the rate of overall survival was 81% in the trametinib group and 67% in the chemotherapy group despite crossover (hazard ratio for death, 0.54; 95% CI, 0.32 to 0.92; P=0.01).
- Conclusions:
  - Trametinib, as compared with chemotherapy, improved rates of progression-free and overall survival among patients who had metastatic melanoma with a BRAF V600E or V600K mutation

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Flaherty et al, NEJM, 2012

Yagerman et al, JAMA Dermatol, 2014


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- Conclusions:
  - Trametinib, as compared with chemotherapy, improved rates of progression-free and overall survival among patients who had metastatic melanoma with a BRAF V600E or V600K mutation
  - No increase in SCCs were noted

Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma

- 97 MM pts (81 with cutaneous MM)
- BRAF Status (36 mutant, 39 wild-type, 6 unknown)
- PFS was 5.7 months
- 4 of 39 BRAF wild-type melanoma pts had partial responses (10%).
- Most common AE was rash or acneiform dermatitis (82%)
- Conclusions:
  - Clinical activity of trametinib in melanoma exists and results suggest that MEK is a valid therapeutic target

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

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.
Records from 60 patients with advanced desmoplastic melanoma treated with anti PD-1 or anti PD-L1 antibodies were analyzed.
- Objective tumor responses seen in 42/60 pts (70%, 95% CI 57-81%)
- 19/60 pts (32%) with complete response
- IHC analysis of a subset of pts revealed high proportion of PD-L1-positive cells

Conclusions:
- Pts with advanced desmoplastic melanoma may benefit from PD-1 or PD-L1 immune checkpoint blockade therapy
- Benefit likely results from high mutational burden and frequent pre-existing adaptive immune response limited by PD-L1 expression

Safety Profile of Nivolumab Monotherapy:
Pooled Analysis of Patients With Advanced MM
- 576 patients, 71% experienced any-grade treatment-related AEs (most commonly fatigue [25%), pruritus [17%), diarrhea [13%), and rash [13%])
- 10% experienced grade 3 to 4 treatment-related AEs
- AEs (occurring in 49% of patients) were most frequently skin related

Conclusions:
- Treatment-related AEs with nivolumab monotherapy were primarily low grade, and most resolved with established safety guidelines

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
Safety Profile of Nivolumab Monotherapy in Patients With Advanced Melanoma

![Graph showing the safety profile of Nivolumab](image)

Weber et al, JCO, 2017

Gut microbiome influences efficacy of PD-1–based immunotherapy

- Melanoma patients receiving PD-1 blockade and found a greater abundance of “good” bacteria in the guts of responding patients.
- Non responders had an imbalance in gut flora composition, which correlated with impaired immune cell activity.
- Conclusions:
  - Maintaining healthy gut flora could help PD-1 patients combat MM
  - The use of antibiotics in MM pts on PD-1 therapy should be carefully considered.

Routy, Science, 2018

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


Improved Survival with ipilimumab in Patients with Metastatic Melanoma


The risk of rash associated with ipilimumab

- Dermatologic adverse events such as rash, pruritus, and vitiligo have been reported in trials, with varying incidences
- 1208 pts from clinical trials were included in this analysis. The overall incidence of all-grade rash was 24.3% (RR=4)
- The overall incidence of high-grade rash was 2.4% (RR=3.3)
- Conclusions:
  - Significant risk of developing rash in patients receiving ipilimumab

Minkis et al, JAAD, 2013
Targeted Antitumor Therapy

Immune Checkpoint Blockade

Targeted Therapies for Melanoma

Table 1: Immune-Checkpoint-Targeting Antibodies Approved by the FDA and Their Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, non-small cell lung cancer, renal cell</td>
</tr>
<tr>
<td>Pembrolizum</td>
<td>PD-L1</td>
<td>Melanoma, non-small cell lung cancer, renal cell</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1 (anti-PD-L1 and anti-PD-1)</td>
<td>Non-small cell lung cancer, metastatic cancers</td>
</tr>
</tbody>
</table>

mab = monoclonal antibody

Postow et al, NEJM, 2018

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

- Cohort study examining 92 pts with metastatic melanoma treated with ipilimumab, nivolumab, or pembrolizumab from January 2007 to February 2016
- Outcomes examined according to age
  - 54 pts ≤65
  - 38 pts >65
- Mean f/u duration following treatment initiation was 12.5 months
- Patients older than 65 treated with immunotherapy had better progression-free survival (4.8 vs 3.4 months, p=0.04) and overall survival (not reached vs 10.1 months, p=0.001) in univariate and adjusted multivariate models

Perier-Muzet et al. JAMA Dermatol, 2018

Association of Checkpoint Inhibitor Therapy with age of Melanoma Pts

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- Outcomes examined according to age
  - 54 pts ≤65
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- Mean f/u duration following treatment initiation was 12.5 months
- Patients older than 65 treated with immunotherapy had better progression-free survival (4.8 vs 3.4 months, p=0.04) and overall survival (not reached vs 10.1 months, p=0.001) in univariate and adjusted multivariate models
- Conclusion:
  - Age may be associated with improved outcomes following immunotherapy treatment for metastatic melanoma without an increased risk of immune-related adverse events

Perier-Muzet et al. JAMA Dermatol, 2018
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

- The addition of nivolumab (anti–PD-1) to ipilimumab (anti–CTLA-4) did not further improve response rate or progression-free survival among patients with PD-L1–positive tumors.
- The combination was much more effective in patients with PD-L1–negative tumors.

Conclusions:
- Among previously untreated patients with metastatic melanoma, nivolumab alone or combined with ipilimumab resulted in significantly longer progression-free survival than ipilimumab alone.
- In patients with PD-L1–negative tumors, the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone.

Overall Survival with Combined Nivolumab and Ipilimumab in Advanced MM

- Randomly assigned 1:1:1 ratio, pts with previously untreated advanced MM to receive nivolumab at a dose of 1 mg/kg plus ipilimumab 3 mg/kg q 3 weeks for four doses, followed by nivolumab at a dose of 3 mg/kg q 2 weeks; nivolumab at 3 mg/kg q 2 weeks plus placebo; or ipilimumab at a dose of 3 mg/kg q 3 weeks for four doses plus placebo.
- Overall survival rate at 3 years:
  - 58% in the nivolumab-plus-ipilimumab group
  - 52% in the nivolumab group
  - 34% in the ipilimumab group
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- Overall survival rate at 3 years:
  - 58% in the nivolumab-plus-ipilimumab group
  - 52% in the nivolumab group
  - 34% in the ipilimumab group
- Conclusions:
  - Combination therapy better than individual checkpoint therapy

Cobimetinib + Atezo: Reduction in Tumor Burden

- Best overall response
  - Maximum Reduction in Sum of Longest Diameters From Baseline, %
  - 15 (75%) patients experienced tumor reduction
  - 2 (10%) patients with confirmed PRs had complete disappearance of target lesions

Targeted Therapies for Melanoma

- BRAF MEK CTLA-4 PD-1
- Targeted Antitumor Therapy Immune Checkpoint Blockade
- Vemurafenib Trametinib Ipilimumab Nivolumab
- Dabrafenib Cobimetinib Pembrolizumab
- Epacadostat Atezolizumab

Epacadostat + Pembrolizumab

- Change in Tumor Burden in Patients with Treatment-Naive Melanoma
  - Best percentage change in target lesions for patients with post-baseline assessments
**Pembrolizumab in Combination With Dabrafenib and Trametinib**

*Longitudinal Change From Baseline in Tumor Size*

*Maximum Percentage Change From Baseline in Tumor Size*

[Graphs showing tumor size change over time and percentage change from baseline.]


**Vem + Cobimetinib + Atezo**

*Reduction in Tumor Burden*

5 patients had a 100% 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*

Higher LDH has a lower response rate.

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

[Graphs showing association between neoeptipote signature and clinical benefit.]


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

[Graphs showing survival in different conditions with and without signature.]
**How close are we to a cure?**

New immunotherapy drug behind Jimmy Carter’s cancer cure

---

**Nivolumab plus ipilimumab in pts with advanced melanoma**

- Long-term (3-year) follow-up of 94 pts with unresectable stage III/IV MM and an ECOG performance status of 0 or 1
- Pts treated with nivolumab plus ipilimumab q3 weeks x4 doses followed by nivolumab q3 weeks x4 doses, followed by nivolumab plus ipilimumab q12 weeks x8 doses or nivolumab plus ipilimumab q3 weeks x4 doses followed by nivolumab q2 weeks
- 3-year overall survival rate was 63%
- Objective response rate by modified WHO criteria was 42%
- 59% experienced grade 3-4 adverse events
- 1 treatment-related death occurred

---

**Conclusion:**

- Survival outcomes for combination of nivolumab plus ipilimumab for advanced melanoma is encouraging, with 3-year survival rates exceeding 60%

---

**Nivolumab Phase Ib 7 year Follow-up:**

Overall survival plateaus at 3 years
**Melanoma**

The future

**Melanoma 2017**

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