Systemic implications of Melanoma

Key issues in Melanoma

Epidemiology:
Incidence and Mortality

Skin Cancer USA - 2018

Cancer USA - 2018

Melanoma - USA

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY
Darrell S, Rigel, MD
Systemic Implications of Melanoma
Key issues you need to know

Castle – A, H, I

Skin Cancer USA - 2018

More Skin Cancers than all other cancers combined

Melanoma - USA

Rigel et al. NYU Melanoma Cooperative Group, 2018
Melanoma – US 2018

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

US Annual Deaths from Melanoma

Skin Cancer Deaths US - 2018

Over 1 American dies of Melanoma every hour

MM Survival – US
Trends over time

Siegel et al, Ca J Clinicians, 2018

1/24

Rigel et al, NYU Melanoma Cooperative Group, 2018
New Challenges in SLNBx

• Database of patients with primary cutaneous melanomas undergoing SLNBx. An independent dataset from MSLT-1 was used for validation
• Early and delayed SLNBx were defined as less than 30 and 30 or more days from initial diagnosis
• No difference in melanoma-specific survival or disease-free survival between those undergoing early or delayed SLNBx
• Conclusions:
  – No adverse impact on long-term clinical outcomes of patients due to delay of SLNB beyond 30 days.
  – Patients can be reassured that if the operation is performed 30 or more days after diagnosis, it will not cause harm.


Impact of Time Between Diagnosis and SLNBx on Outcomes in MM

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

NCCN SLNBx recommendations (2018):

Mitotic rate is associated with positive SLN in thin MM

• 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)

Mitotic rate is associated with positive SLN in thin melanomas

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• 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

Mitotic rate is associated with positive SLN in thin melanomas

Wheles et al. JAAD, 2017

Wheles et al. JAAD, 2017

Karia et al. JAMA Dermatol, 2017

Karia et al. JAMA Dermatol, 2017
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?

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

- Thin MM:
  - Routine SLNBx is not recommended for patients with MM 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 MM:
  - SLNBx is recommended for patients with MM that are T2 or T3 (1.0 to 4.0mm)

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

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

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.
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.

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

**Genetics**

**Prognosis**

**Therapy**

**PD-L1 expression and Desmoplastic MM aggressiveness and progression**

- Tumoral PDL1 expression (≥25%), which was seen in 21% of patients (14 of 66), significantly correlated with mixed histology, tumor thickness, mitoses, recurrence, and metastasis.

- According to multivariate analyses, PD-L1 expression of 25% or more (P = .026) and mixed histology (P = .039) independently predicted shorter progression-free survival, and presence of lympho-vascular invasion predicted shorter overall survival (P = .018).

**PD-L1 expression and Desmoplastic MM aggressiveness and progression**
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- Conclusions:
  - PD-L1 expression in desmoplastic melanoma was associated with tumor aggressiveness and progression.
  - PD-L1 frequency and level of expression in desmoplastic melanoma may identify a subset of melanomas that are likely to respond to immunotherapy.

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

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**Invasive MM US Cases by Thickness**

- SEER 1992-2003

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1mm</td>
<td>72%</td>
</tr>
<tr>
<td>1-1.99mm</td>
<td>16%</td>
</tr>
<tr>
<td>2-3.99mm</td>
<td>8%</td>
</tr>
<tr>
<td>4+mm</td>
<td>8%</td>
</tr>
</tbody>
</table>

Landow et al, SID poster, 2016

**Invasive MM US Deaths by Thickness**

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<table>
<thead>
<tr>
<th>Thickness</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1mm</td>
<td>29%</td>
</tr>
<tr>
<td>1-1.99mm</td>
<td>27%</td>
</tr>
<tr>
<td>2-3.99mm</td>
<td>17%</td>
</tr>
<tr>
<td>4+mm</td>
<td>27%</td>
</tr>
</tbody>
</table>

Landow et al, SID poster, 2016

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**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

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**Clinical Issue in Early Stage Melanoma**

- All newer therapies and regional interventions are effective in metastatic melanoma.
- Within Stage IV and resected Stage III disease, early intervention is consistently shown to be a (or in many cases the most) significant predictor of response 1, 2, 3, 4, 5, 6, 7
- While AJCC clinicopathologic factors are good 9 majority of deaths occur in early stage disease 5, 8, 9
- 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
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

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

<table>
<thead>
<tr>
<th>Primary melanoma tumor tissue</th>
<th>RNA isolation</th>
<th>cDNA generation and amplification (14X)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Microfluidics PCR gene card</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analysis of GEP with a proprietary algorithm to determine class and metastatic risk</td>
</tr>
<tr>
<td>Class 1</td>
<td>low metastatic risk</td>
<td>Class 2 high metastatic risk</td>
</tr>
</tbody>
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- Uses in formalin-fixed, paraffin-embedded tissue specimen obtained from primary biopsy
- That is, no special processing on behalf of the dermatologist or dermatopathologist
- Validated binary algorithm identifies likelihood of developing recurrence/metastasis within 5 years:
  - Low risk Class 1 profile or
  - High risk Class 2 profile
**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

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**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.

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

- **DMFS**
  - SLNB
    - **Class 1**
    - **Class 2**
    - Events: 10, 43, 5-yr DMFS: 86%, 49%
  - SLNB+ (n=58)
    - Events: 53, 32
    - 5-yr DMFS: 64%, 42%

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**Impact of a test on management**

- **Info**
- **+ test**
Impact of the 31-GEP test on management

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

Would you do a SLNBx?

<table>
<thead>
<tr>
<th></th>
<th>No GEP provided</th>
<th>Class 1</th>
<th>Class 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>55%</td>
<td>34%*</td>
<td>85%*</td>
</tr>
</tbody>
</table>

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

Would you pursue imaging?

<table>
<thead>
<tr>
<th></th>
<th>No GEP provided</th>
<th>Class 1</th>
<th>Class 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>31%</td>
<td>18%*</td>
<td>65%*</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow depth</td>
<td>0.4 (0.01-1.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>1.1 (0.9-1.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Ulceration</td>
<td>3.7 (1.0-14.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>SLN status</td>
<td>2.1 (0.5-8.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>GEP Class 2</td>
<td>5.4 (1.2-23.5)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*no factors significant in multivariate models for DMFS or MSS.

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 younger patients are SLN positive.
  - Likewise, a negative SLNB in head and neck melanomas 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?
  - ≤5% SLNB positivity rate is often considered an adequate threshold for considering this procedure.

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?

<table>
<thead>
<tr>
<th>Decision/OS</th>
<th>MSS</th>
<th>DS</th>
<th>DMFS</th>
<th>RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 No SLNB</td>
<td>96.3%</td>
<td>97.2%</td>
<td>93.4%</td>
<td>91.7%</td>
</tr>
<tr>
<td>SLN Neg</td>
<td>96.3%</td>
<td>95.3%</td>
<td>86.3%</td>
<td>77.2%</td>
</tr>
<tr>
<td>SLN Pos</td>
<td>73.6%</td>
<td>52.4%</td>
<td>32.3%</td>
<td>47.6%</td>
</tr>
</tbody>
</table>

Patient with T1/T2 Melanoma

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>
<td>Prostate cancer</td>
<td>Rule-out repeat biopsies after negative prostate biopsy</td>
<td>90%</td>
</tr>
<tr>
<td>Percepta</td>
<td>Lung cancer</td>
<td>Rule-out invasive procedures after bronchoscopy</td>
<td>91%</td>
</tr>
<tr>
<td>Afirma</td>
<td>Thyroid cancer</td>
<td>Rule-out surgery for indeterminate thyroid nodules</td>
<td>94%</td>
</tr>
<tr>
<td>Thrymr</td>
<td>Thyroid cancer</td>
<td>Rule-out surgery for indeterminate thyroid nodules</td>
<td>94%</td>
</tr>
<tr>
<td>Melanoma 31-GEP</td>
<td>Cutaneous melanoma</td>
<td>Rule-out SLNB biopsy in cutaneous melanoma</td>
<td>90%*</td>
</tr>
</tbody>
</table>

*≥65 year old patient

Melanoma Vaccine Approaches

Polyvalent

2010

The end...

Personalized Medicine

Targeted Therapy for Melanoma
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

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Normal</th>
<th>V600E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu</td>
<td>Glu</td>
<td>Val</td>
</tr>
</tbody>
</table>

V600E mutation

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Normal</th>
<th>V600E</th>
</tr>
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<tbody>
<tr>
<td>Glu</td>
<td>Glu</td>
<td>Val</td>
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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.

Chapman et al, NEJM, 2010
Development of SCCs in MM pts on Vemurafenib

- BRAF functions in the signaling cascade between RAS (upstream) and ERK (downstream)
- Drug induces KA/SCCs that do not have BRAF mutations
- But 60% of the KA/SCCs produced have RAS mutations (vs 3-40% in other SCCs)

Su et al, NEJM, 2012

PDT for Multiple Eruptive Keratoacanthomas Associated With Vemurafenib Treatment for Metastatic MM

- Pt with stage IV melanoma who received the BRAF inhibitor vemurafenib as part of a clinical trial and developed numerous diffuse, pathology-proven KAs and SCCs
- Too many to remove surgically
- Compared with untreated tumors, most lesions demonstrated significant clinical regression following successive cycles of PDT
- Conclusion:
  - PDT is a potentially useful choice for initial treatment of KAs arising after BRAF inhibitor therapy when surgical excision of all lesions is often impractical

Albo et al, JAMA Dermatol, 2012

Dabrafenib in BRAF-mutated metastatic MM multcenter, open-label, phase 3 trial

- 250 pts were randomly assigned to receive either dabrafenib (187 pts) or dacarbazine (63 pts)
- Median progression-free survival was 5.1 months for dabrafenib and 2.7 months for dacarbazine
- AEs occurred in 53% of the pts on dabrafenib and in 44% of the pts who received dacarbazine.
- Most common adverse events with dabrafenib were skin-related toxic effects
- Conclusions:
  - Dabrafenib significantly improved progression-free survival compared with dacarbazine

Hauschild et al, Lancet, 2012

Melanoma Growth Pathways

MAPK pathways

Hauschild et al, Lancet, 2012
BRAF and NRAS mutations in MM

- BRAF mutations found in:
  - 41% of MMs
  - RR=2 SSM, RR=2 non-chronic sun exposed skin
- NRAS mutations found in:
  - 17% of MMs
  - RR=1.9 SSM, RR=1.9 chronic sun exposed skin
- BRAF and NRAS mutations are mutually exclusive

Conclusions:
- Melanoma may be more than one cancer
- Different pathways may be in effect for the growth of Melanoma

Lee et al, Br J Dermatol, 2011

NRAS Biology

Normal amino acid sequence

<table>
<thead>
<tr>
<th>Codon 61 Q61R (CAA/CGA) and Q61K (CAA/AAA)</th>
</tr>
</thead>
</table>

NRAS → MM Growth

Locks RAS into the active signaling position so it continuously drives alternate pathway independent of other inputs

Debarbieux et al, Br J Dermatol, 2013

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.


Second primary MMs under BRAF blockers: study by Reflectance Confocal Microscopy

- 10 pigmented lesions with no pre-existing atypia by RCM re-examined 3 months after treatment with vemurafenib
- RCM pattern identified in 5 lesions characterized by areas of marked atypias in otherwise previously non dysplastic lesions
- 4 of these lesions found to be MMs
- Conclusion:
  - RCM examinations confirmed that microscopic marked atypias that led to the histopathological diagnosis of MM appeared under treatment and were not preexisting

Debarbieux et al, Br J Dermatol, 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

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
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  - 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

Yagerman et al, JAMA Dermatol, 2014
**Improved survival with MEK inhibition by treatment 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
- No increase in SCCs were noted

Flaherty et al, NEJM, 2012

**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 acneform dermatitis (82%)

**Conclusions:**
- Clinical activity of trametinib in melanoma exists and results suggest that MEK is a valid therapeutic target

Falchook et al, Lancet, 2013

**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
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, colitis, hepatitis, hypophysitis, and thyroiditis


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

- 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.

FDA 2016

Pembrolizumab versus Ipilimumab in Advanced Melanoma

- Pembrolizumab is a PD-1 inhibitor that is indicated for advanced MM
- Pembrolizumab produced significantly improved progression-free and overall survival and less high-grade toxicity than did ipilimumab in patients with metastatic melanoma.
- 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.

Robert et al, NEJM, 2015
**Overall Survival for Pembrolizumab Versus Ipilimumab**

Keynote -006: Updated

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Pembro Q2W</td>
<td>122</td>
<td>0.68 (0.53-0.87)</td>
<td>0.00085</td>
</tr>
<tr>
<td>Pembro Q3W</td>
<td>119</td>
<td>0.68 (0.53-0.86)</td>
<td>0.00083</td>
</tr>
<tr>
<td>Ipi</td>
<td>142</td>
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</tr>
</tbody>
</table>

Schachter, J et al ASCO 2016

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**PD-1 blockade in the treatment of advanced desmoplastic melanoma**

- 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

Faries et al. Nature, 2018

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**PD-1 blockade in the treatment of advanced desmoplastic melanoma**

- Images of three cases of desmoplastic melanoma that responded to PD-1 blockade therapy
- 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

Faries et al. Nature, 2018

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**Safety Profile of Nivolumab Monotherapy**

- 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**

- Lichenoid Reaction
- Eczema
- Vitiligo

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

Huang et al., J Am Acad Dermatol, 2016

**Safety Profile of Nivolumab Monotherapy in Patients With Advanced Melanoma**

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

**Ipilimumab**

- Human monoclonal antibody that binds to CTLA-4 (cytotoxic T lymphocyte-associated antigen 4)
- Anti-CTLA-4 antibodies enhance T cell responses and activate proliferation of tumor-specific T cells
- Blockade of CTLA-4 by ipilimumab leads to immune-mediated tumor regression
- Phase III, multi-center, randomized, double-blind trial showed a significant improvement in overall survival in patients with advanced melanomas treated with ipilimumab

Lara et al., Curr Top Med Chem 2011
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

Targeted Therapies for Melanoma

Targeted Antitumor Therapy

<table>
<thead>
<tr>
<th>Target</th>
<th>BRAF</th>
<th>MEK</th>
<th>CTLA-4</th>
<th>PD-1</th>
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mab = monoclonal antibody

Immune Checkpoint Blockade

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Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
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<tr>
<td>Ipilimumab</td>
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<td>Melanoma</td>
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<tr>
<td>pembrolizumab</td>
<td>PD-L1</td>
<td>Melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, nasopharyngeal carcinoma, urothelial carcinoma, and glioblastoma multiforme</td>
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<td>PD-L1</td>
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IDO1 = indoleamine 2,3-dioxygenase

Postow et al, NEJM, 2018
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

Conclusion:
- Age may be associated with improved outcomes following immunotherapy treatment for metastatic melanoma without an increased risk of immune-related adverse events

Potential Advantage of Combination Therapy

Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations

Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma
**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 x 4 doses followed by nivolumab q3 weeks x 4 doses, followed by nivolumab plus ipilimumab q12 weeks x 8 doses or nivolumab plus ipilimumab q3 weeks x 4 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

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

Callahan et al. J Clin Oncol, 2018

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**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.

Larkin et al, NEJM, 2015

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**Nivo + Ipi vs Ipi in Advanced Melanoma**

**Checkmate-069 OS at 2 Years of Follow-Up**

All Randomized Patients

Larkin et al, NEJM, 2015

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**Postow M, et al. AACR. 2016.**
**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

**Conclusions:**
- Combination therapy better than individual checkpoint therapy.

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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

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

Association of a Neopitope 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

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How close are we to a cure?

Nivolumab Phase Ib 7 year Follow-up:

Overall survival plateaus at 3 years
Remember…
Advances in melanoma impact patients

Summary
• Melanoma rates rising and absolute numbers of thick lesions increasing
• Therapy targets growing
• Genetics playing an increasing role
• Getting closer to a “cure” for melanoma?