What You Need to Know about Advanced Melanoma Therapies – Targeted Approaches

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Susan M. Swetter, MD

S021 Dilemmas and Challenges in Skin Cancer Therapies and Management

DISCLOSURES

I do not have any relevant relationships with industry.
Where we came from...

An Era of Futility: 1975-2005

1980

DTIC

High-dose IL-2

1975

2005

Korn et al. J Clin Oncol 2009

Median survival 6.2 mos; 25% pts alive at one year

Courtesy of Ryan Sullivan, MD
During the “Era of Futility” - 2 fundamental and translatable discoveries occurred:

- Sullivan and Flaherty. Clin Cancer Res. 2015
- Melanoma TCGA. Cell 2015
- Sullivan et al. ASCO Ed Book 2015
- Melanoma TCGA. Cell 2015
Changing Melanoma Treatment Landscape

- **1980**: DTIC
- **2011**: Ipilimumab
- **2013**: Vemurafenib (V), Dabrafenib (D), Trametinib (T)
- **2015**: Nivolumab, Pembrolizumab, Ipi + Nivo
- **2016**: Binimetinib, Encorafenib

**Median survival 2016**: 20-32 mos!

*Courtesy of Ryan Sullivan, MD*
Systemic Therapy for Metastatic Melanoma

- **Targeted therapy**
  - BRAF inhibitors
    - dabrafenib
    - vemurafenib
  - MEK inhibitors
    - trametinib
    - cobimetinib

- **Immunotherapy**
  - Anti CTLA-4
    - ipilimumab
  - Anti PD-1
    - pembrolizumab
    - nivolumab

“Regular dermatologic evaluation and referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of targeted therapy is recommended.”

“Immune-mediated dermatitis often responds to topical corticosteroids. For immune-mediated dermatitis that does not respond, or for patients who have a history of immune-mediated skin disorders such as psoriasis or autoimmune blistering disease, consider referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of immunotherapy.”

Targeted Therapy with MAP Kinase inhibitors

- **Targeted therapy**
  - BRAF inhibitors
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    - vemurafenib
  - MEK inhibitors
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    - cobimetinib

- **Immunotherapy**
  - Anti CTLA-4
    - Ipilimumab
  - Anti PD-1
    - pembrolizumab
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- Small molecule inhibitors
- Interfere with specific molecules involved in cancer cell growth and survival
Combination BRAF/MEK inhibitors

Dabrafenib + Trametinib
Vemurafenib + Cobimetinib

Combination BRAF/MEK inhibitor results in significant reduction in cutaneous toxicities compared with the incidence with BRAF or MEK inhibitors alone

NCCN 2018: “BRAF inhibitors are associated with cutaneous SCC, extreme photosensitivity, and other dermatologic toxicities, which occur much less often with concurrent MEK inhibitors.”

BRAF inhibitors

- **Targeted therapy**
  - **BRAF inhibitors**
    - dabrafenib
    - vemurafenib
  - **MEK inhibitors**
    - trametinib
    - cobimetinib
- **Immunotherapy**
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~1/2 of patients with metastatic melanoma harbor activating BRAF mutation

Being studied in the adjuvant setting (resected stage II/III melanoma)
BRAF inhibitors: multiple cutaneous toxic effects

Hyperkeratotic Lesions

Keratosis pilaris-like eruption

Seborrheic dermatitis-like hyperkeratotic/cystic facial eruption

Hyperkeratotic hand-foot skin reaction (mimicking sorafenib-induced reaction)

Eruptive cutaneous SCCs and KAs

BRAF inhibitor related verrucal keratoses, eruptive cutaneous SCCs and KAs:

- Median time to presentation ~8 wks
- SCC incidence
  - 4–31% (vemurafenib)
  - 6–11% (dabrafenib)

BRAF inhibitor related verrucal keratoses, eruptive cutaneous SCCs and KAs

Management:

- full skin check at baseline, prior to treatment initiation
- Regular skin checks with local destruction with cryotherapy to early/small hyperkeratotic lesions. May also use keratolytics, topical retinoids, topical 5-fluoro-uracil cream
- conservative surgical intervention
- watch and wait
- *concomitant MEK inhibitor*
BRAF inhibitor related UVA-mediated phototoxicity

Management: strict avoidance of sun, broad spectrum sun protection (chemical > physical sunscreens, partic Tinosorb®-containing agents)

Livinstone et al. CCO. March 2014; Dummer R et al. NEJM 2012
BRAF inhibitor-related
Hyperkeratotic hand-foot skin reaction

Management: preemptive treatment of underlying calluses/xerosis prior to initiation of medication, rest/avoid trauma, thick socks, keratolytics, high potency topical steroids, topical lidocaine for pain, partnership with podiatry
BRAF inhibitor related radiation recall and enhanced radiation dermatitis

Management: Recognition of this potential side effect in patients who have history of prior radiation therapy, or who may be undergoing concomitant radiotherapy (for brain metastases, palliative/bony pain). Topical steroids, supportive care (NSAIDS, emolliation)

Kuo KY et al. Cutis. 2016;98:E4-6
• Targeted therapy
  – BRAF inhibitors
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    • vemurefenib
  – MEK inhibitors
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    • cobimetinib

• Immunotherapy
  – Anti CTLA-4
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  – Anti PD-1
    • pembrolizumab
    • nivolumab

• oral small molecule inhibitor of MEK1 and MEK2, downstream of BRAF
MEK inhibitor related papulopustular eruption

- similar to those of EGFR inhibitors
- Papulopustular/acneiform eruption in 52-93% of patients
- secondary superinfection may occur, commonly Staphylococcus aureus

Management: similar to EGFR inhibitor-induced cutaneous adverse events

Systemic Therapy for Advanced or Metastatic Melanoma: Immunotherapy

- Immune checkpoint inhibitors, aka checkpoint blockade

**Targeted therapy**
- BRAF inhibitors
  - dabrafenib
  - vemurefenib
- MEK inhibitors
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  - cobimetinib

**Immunotherapy**
- Anti CTLA-4
  - ipilimumab
- Anti PD-1
  - pembrolizumab
  - nivolumab
Key Developments in Melanoma Immunotherapy Occurred in Tandem with Targeted Therapy Approaches

Inhibition of Immune Checkpoints:
- Creation of blocking antibodies against:
  - CTLA-4
  - PD-1
  - PD-L1

“Takes the breaks off” the immune system
Ipilimumab

- Monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4)
  - Increased T-cell activation and cytokine secretion
- FDA approved March 2011 for treatment of metastatic melanoma
- First agent to demonstrate increased overall survival compared to dacarbazine
- Substantial risk of immune-related reactions (60% in pivotal trial), including deaths
  - skin (pruritus, rash) and gastrointestinal tract (diarrhea colitis) side effects most frequently reported, endocrinopathies are permanent

Hodi FS et al. NEJM. 2010;363:711
Ipilimumab (ipi) – first novel immunotherapy agent to show prolonged survival in melanoma

Sullivan and Flaherty. Clin Cancer Res. 2015

Hodi et al. NEJM 2010

Robert et al. NEJM 2011

Hodi et al. ECCO 2014
Systemic Therapy for Advanced or Metastatic Melanoma: **ipilimumab**

- **Targeted therapy**
  - BRAF inhibitors
    - dabrafenib
    - vemurafenib
  - MEK inhibitors
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- **Immunotherapy**
  - **Anti CTLA-4**
    - **ipilimumab**
  - **Anti PD-1**
    - pembrolizumab
    - nivolumab

  - Substantial risk of immune-related adverse events (irAEs) (64%)
    - skin (pruritus, rash) and gastrointestinal tract (diarrhea/colitis) side effects most frequently reported
  - Dermatologic events manifest earlier in treatment than other irAEs
  - Gen include: nonspecific rash, pruritus, and vitiligo

Lacouture M et al. JAAD 2014; Hodi S et al. NEJM. 2010
Ipilimumab related morbilliform dermatitis

- 24.3% incidence all-grade rash
  - reticular, erythematous, edematous, maculopapular
  - may be pronounced around nevi, suggesting inflammatory response toward melanocytes
- +/- pruritus
- +/- peripheral eosinophilia
- histology nonspecific
- median time to onset of 3-4 weeks (range up to 17.3 weeks—should be followed)
  - Shorter time to onset than GI, liver, or endocrine system symptoms

Ipilimumab related morbilliform dermatitis

Ipilimumab related pruritus

- ~30% incidence
- negative impact on quality of life
- not necessarily accompanied by visible rash

Management of skin pruritus associated with ipilimumab

- **Pruritus Mild or Localized**
  - Topical corticosteroids, antipruritics

- **Intense or Widespread - Intermittent**
  - Skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); topical corticosteroids and oral antihistamines indicated; limiting instrumental ADL

- **Intense or Widespread - Constant**
  - Limiting self-care ADL or sleep; oral antihistamines and corticosteroids indicated, consider gabapentin, pregabalin, mirtazapine, aripiprazole

Lacouture M et al. JAAD 2014
Ipilimumab related vitiligo-like melanoma-associated hypopigmentation (MAH)

- asymptomatic
- possibly portends prognostic favorability
- Management: sun protection, camouflage, make-up/cover-up
- Persists after drug cessation

Courtesy: Bernice Kwong, MD
Pembrolizumab/Nivolumab

- Monoclonal antibody that binds to the PD-1 (programmed cell death-1) receptor
  - Blocks interaction of PD-1 with its ligands: PD-L1 and PD-L2
  - Releases PD-1 pathway-mediated inhibition of the immune system to increase antitumor immune response
  - FDA approved pembro in September 2014 for patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF-mutant, a BRAF inhibitor
  - Approved as 1st line monotherapy in 2015
  - >80% of patients alive at 2 yrs
Anti PD-1 antibodies (aka PD-1 inhibitors)

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  - Anti PD-1
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- Monoclonal antibodies that bind to the PD-1 (programmed cell death-1) receptor
- Anti PD-1 related cutaneous adverse events (49%)
  - Includes nonspecific rash, vitiligo, lichenoid dermatitis, bullous pemphigoid, psoriasiform dermatitis, 9% grade 3-4
  - delayed reactions (immunotherapy requires more time to induce immune responses)
  - cutaneous AEs associated with significantly longer progression-free survival

Anti PD-1 antibody therapy related vitiligo

- 11-25% incidence
- time to onset: 52-453 days (median 126 days)
- immune-mediated destruction through recognition of melanoma-associated antigens shared by normal melanocytes and melanoma cells
- Management: sun protection


Courtesy: Silvina Pugliese, MD
Development of vitiligo associated with improved outcome

- 67 patients, 25% developed vitiligo
- All vitiligo patients alive at 441 days
- Higher objective response (complete or partial) in those who developed vitiligo (71%) vs those who didn’t (28%)

<table>
<thead>
<tr>
<th>Table 2. Response to Treatment at Final Follow-up</th>
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<tbody>
<tr>
<td>Patient Group</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Vitiligo (n = 17)</td>
</tr>
<tr>
<td>3 (18)</td>
</tr>
<tr>
<td>No vitiligo (n = 50)</td>
</tr>
<tr>
<td>All (N = 67)</td>
</tr>
</tbody>
</table>

* The difference between the vitiligo and nonvitiligo groups in objective (complete and partial) response (12 of 17 [71%] vs 14 of 50 [28%]) was significant (Fisher exact test, P = .002)
Anti PD-1/PD-L1 related lichenoid dermatitis

- 75% with pruritus
- Variable time of onset (mean 4 mos) – delayed compared to ipi
- Variable clinical presentation (even in same patient)
- Pathology strikingly consistent: lichenoid infiltrate with more spongiosis and epidermal necrosis than LP
- Gen responds to topical steroids

Anti-PD1/PD-L1 related lichenoid dermatitis

Management:
topical steroids (under occlusion)

Courtesy: Stanford Dermatopathology and Bernice Kwong, MD
Anti-PD1/PD-L1 related lichenoid mucositis

Management: dexamethasone elixir swish/spit; clobetasol ointment to vulva

Courtesy: Stanford Dermatopathology and Bernice Kwong, MD
Dual anti-PD1/anti-CTLA4 (nivo + ipi) therapy is associated with higher RR

Wolchok et al. NEJM 2013

Sullivan and Flaherty. Clin Cancer Res. 2015
Checkmate 067 - Combination: 
*ipi + nivo is associated with increased toxicity*

Safety Summary at 3 years

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Treatment-related adverse event (AE)</td>
<td>96%</td>
<td>59%</td>
<td>86%</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>39%</td>
<td>30%</td>
<td>12%</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Two reported in the NIVO group (neutropenia) and one in the IPI group (colonic perforation) 2 deaths in NIVO/IPI (cardiac insufficiency/autoimmune myocarditis and liver necrosis).*

Talimogene Laherparavec (T-VEC)

• Viral oncolytic immunotherapy
• Newer approach to treating certain melanomas (cutaneous, in-transit, nodal mets) in the outpatient clinical setting
  – based on herpes simplex virus type 1
  – administered via intra-tumoral injection to in-transit or nodal mets
  – induces viral lysis of melanoma cells, followed by stimulation of a tumor-specific immune response
  – risk of spread to people in close contact with the patient following administration, vulnerable populations or through accidental exposure
  – Specific bio-safety procedures and processes are required

Comparison of systemic therapy for advanced* melanoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR</th>
<th>PFS (med)</th>
<th>OS (med/2-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-agent BRAFi</td>
<td>50%</td>
<td>6-8 mo</td>
<td>18.7 mo / ~40%</td>
</tr>
<tr>
<td>Combo BRAFi &amp; MEKi (1st line)</td>
<td>65-70%</td>
<td>9-12 mo</td>
<td>25 mo / ~50+%</td>
</tr>
<tr>
<td>Ipilimumab (IPI)</td>
<td>10%</td>
<td>2-3 mo</td>
<td>36 mo / 34%**</td>
</tr>
<tr>
<td>Anti-PD1 Ab (1st line) (NIVO or PEMBRO)</td>
<td>25-45%</td>
<td>~6 mo</td>
<td>36 mo /52%**</td>
</tr>
<tr>
<td>Combo IPI &amp; NIVO (1st line)</td>
<td>~60%</td>
<td>11-12 mo</td>
<td>36 mo /58%**</td>
</tr>
</tbody>
</table>

*Unresectable Stage III or Stage IV melanoma

**Wolchok JD et al. NEJM 2017
Therapeutic landscape for metastatic melanoma continues to rapidly change with development of novel, targeted- and immuno-therapies that demonstrate better efficacy and less toxicity overall.

**HOWEVER, skin toxicity is common!**

Critical for dermatologists to work with oncologists to recognize and manage these toxicities:
- improve patient quality of life
- prevent unnecessary dose reduction or discontinuation of medication