Novel Therapies in Melanoma – the Immunotherapy Approach

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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F002 Novel Therapies for Cutaneous Malignancies: What’s New and What’s Ahead

DISCLOSURES

I do not have any relevant relationships with industry.
Metastatic Melanoma (AJCC Stage IV)

- Distant skin, nodal, visceral, skeletal, or brain metastasis

- Before 2011, survival had not changed appreciably over the prior 30+ years
  - Median survival in 2010: 6-9 months; **in 2016: 20-32 months!**

- Approved agents for unresectable stage III and stage IV melanoma:
  - **DTIC**: RR 6%-8%, no long-term survival benefit
  - **High dose bolus IL-2**: 5-7% durable remission, highly toxic
  - **Ipilimumab (CTLA-4 Ab)**, **Vemurafenib (BRAFi)** - 2011
  - **Dabrafenib (BRAFi)**, **Trametinib (MEKi)** - 2013; **Combination dab/tram** - 2014
  - **Pembrolizumab (PD-1 Ab)** – 2014; **Nivolumab (PD-1 Ab)** – 2015
  - **Vemurafenib/Cobemetinib** (BRAF/MEKi combo); **ipi/nivo combination**; and **Talimogene laherparepvec (T-VEC)** – 2015
  - **Atezolizumab (PD-L1 Ab)** – under investigation
Where we came from…

An Era of Futility: 1975-2005

DTIC

High-dose IL-2

1980

2011

2013

2015

Korn et al. J Clin Oncol 2009

Courtesy of Ryan Sullivan, MD
Overall Survival After Checkpoint Blockade

Percent Alive vs Years

- ipilimumab
- nivolumab + ipilimumab
- PD-1 pathway blockade
- ipilimumab
During the “Era of Futility” - 2 fundamental and translatable discoveries occurred

Sullivan and Flaherty. Clin Cancer Res. 2015

Systemic Therapy for Metastatic Melanoma

The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents which have demonstrated better efficacy than traditional chemotherapy – NCCN guidelines, Melanoma
Changing Melanoma Treatment Landscape

1980

- DTIC
- High-dose IL-2

2011

- Ipilimumab
- Vemurafenib (V)

2013

- Dabrafenib (D), Trametinib (T)
- D + T

2015

- Pembrolizumab
- Nivolumab
- Ipi + Nivo
- Binimetinib, Encorafenib
- Cobimetinib + Vem
- TVEC

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

“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.”

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

Grading of Dermatologic Adverse Events
Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

**Adverse event:** any abnormal clinical finding temporally associated with the use of therapy; causality is not required

**Grade:** refers to the severity of the AE

In general, (*specific parameters according to organ system involved):

**Grade 1: Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

**Grade 2: Moderate;** minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

**Grade 3: Severe** or medically significant but **not immediately life-threatening;** hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). (May result in holding the drug).

**Grade 4: Life-threatening** consequences; urgent intervention indicated.

**Grade 5: Death** related to AE.
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

Sullivan and Flaherty. Clin Cancer Res. 2015
Why do we have negative immune checkpoints?

• Cancer immune inhibitory molecules (CTLA-4, PD-1, PD-L1/L2)

• These negative signals:
  – Maintain immune tolerance
  – Protect tissues from damage by immune response
  – Turn down immune response after elimination of microbes
  – Tumors and microbes exploit these inhibitory signals to prevent immune eradication
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

Robert et al. NEJM 2011
Systemic Therapy for Advanced or Metastatic Melanoma: 

**ipilimumab**

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

- **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
- 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

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  - +/- pruritus
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  - histology nonspecific
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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

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

 Courtesy: Bernice Kwong, MD
Does treatment of irAEs affect outcome?

Study of nearly 300 pts on ipi:
- 85% developed immune-related adverse events (irAEs)
  - Overall survival same in patients with irAEs, including skin reactions, compared with those without an irAEs
  - No difference in survival between patients requiring corticosteroids and those not requiring immunosuppressive therapy for treatment of irAEs

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-PD1 therapy is better than chemo after ipi

Sullivan and Flaherty. Clin Cancer Res. 2015
Ribas et al. Lancet Oncol 2015

Nivolumab showed OS benefit compared to chemotherapy - even after ipilimumab failure
Front-line anti-PD1 therapy better than chemo & ipi

Sullivan and Flaherty. Clin Cancer Res. 2015

Robert et al. NEJM 2014

Robert et al. NEJM 2015
Anti PD-1 antibodies (aka PD-1 inhibitors)

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

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

- 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

PD-1 inhibitors: “Breakthrough” in Melanoma Treatment

• Pembrolizumab - superior to ipilimumab for unresectable advanced melanoma (global KEYNOTE-006 trial)
• Nivolumab and Pembrolizumab are equivalent in efficacy
  – Higher expression of PD-L1 associated with improved response
• Most responses partial – but DURABLE!
  – ~60% maintain disease control in absence of a complete response (CR)
• Requires ongoing tx every 2-3 wks (maybe), more tolerable than ipi
• Bottom line: Melanoma patients are living longer and better with these new treatments
• Side effect management and survivorship issues need to be addressed
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

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 2. Response to Treatment at Final Follow-up

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Complete No. (%) of Patients</th>
<th>Partial No. (%) of Patients</th>
<th>Stable No. (%) of Patients</th>
<th>Progressive No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitiligo (n = 17)</td>
<td>3 (18)</td>
<td>9 (53)</td>
<td>3 (18)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>No vitiligo (n = 50)</td>
<td>4 (8)</td>
<td>10 (20)</td>
<td>1 (2)</td>
<td>35 (70)</td>
</tr>
<tr>
<td>All (N = 67)</td>
<td>7 (10)</td>
<td>19 (28)</td>
<td>4 (6)</td>
<td>37 (55)</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
Delayed lichenoid dermatitis after discontinuation of anti-PD-1 therapy

Courtesy: Bernice Kwong, MD
Management: topical steroids under occlusion when severe presentation

36 hours later after triamcinolone 0.1% ointment with sauna suit occlusion; asymptomatic

Courtesy: Bernice Kwong, MD
Severity of lichenoid dermatitis may worsen over time

Initial solitary lesion 7 weeks after first infusion (8/2014)

12/2014: exquisitely pruritic, more lesions

8/2015; more widespread, severe pruritus

9/2015. 60% BSA

Wolf’s isotopic response

Courtesy: Bernice Kwong, MD
Anti PD-1 antibody therapy related psoriasiform dermatitis

Ohtsuka M et al. JAMA Dermatol. 2015
Anti PD-1 immunotherapy related autoimmune blistering disease

- Can present up to **18 months after starting** therapy
- may persist for several months after discontinuation of the agent
- May not present with vesicles/bullae


Courtesy: Stanford Dermatopathology
Anti PD-1 immunotherapy related autoimmune blistering disease

- **Management:** doxycycline, nicotinamide, topical steroids under occlusion, treatment of secondary infection, systemic steroids, IVIG, methotrexate, tocilizumab, omalizumab *(similar to BP)*


*Courtesy: Stanford Dermatopathology*
Dual anti-PD1/anti-CTLA4 (nivo + ipi) therapy is associated with high RR

Sullivan and Flaherty. Clin Cancer Res. 2015

Wolchok et al. NEJM 2013
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 performation) 2 deaths in NIVO/IPI (cardiac insufficiency/autoimmune myocarditis and liver necrosis).

Combo immunotherapy & BRAF inhibitor: Drug-induced hypersensitivity
Talimogene Laherparavvec (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%** (20% 5 yr survival)</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
Other Novel Immunotherapies and Combinations

Bench (or early trials)

- **PD-L1 blockers:** VERY PROMISING
  - Monotherapy
  - Combined with targeted or other checkpoint inhibitors
- **Inhibitors of negative regulators in tumor microenvironment**
  - Indoleamine dioxygenase inhibitor
  - Inhibitors of suppressive cells like certain myeloid cells and Treg cells
- **Immune costimulation**
  - 4-1BB- or OX-40 or CD40L agonistic Ab
  - GM-CSF with checkpoint blockers
- **Vaccines?**—still very challenging

Bedside (later trials)

- **CTLA-4 Ab +/- bevacizumab**
- **CTLA-4 Ab + PD-1 Ab +/- GM-CSF**
- **Other γc cytokines**
  - IL-15 + PD-1 blockade
  - IL-7 + various adoptive T cell Rxs
- **CTLA-4 Ab and/or PD-1 Ab plus radiotherapy** (abscopal effect) or T-vec
- **Enhancers of ADCC**
- **Lesional, regional delivery**
  - Viral→ immunomodulatory genes
  - Cytokines, DC activators
  - Systemically toxic checkpoint inhibitor like ipilimumab

Courtesy of Kim Margolin, MD
Conclusion

- 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