The melanoma revolution: immune and targeted therapies

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870 new cases of invasive melanoma in the US predicted for 2015

5,480 cases predicted for Florida*

* Second-most cases of any state in the US after California, (8,560 cases); New York third (4,270 cases)
The Melanoma Revolution
FDA Approved Agents

Before 2011
- carbazine (1970s)
- Response rate <10%
- Time to progression 2 months
- Median survival 10 months
- One-year survival ~25%
- interferon-alfa (1995)

Since 2011
- Ipilimumab
- Vemurafenib
- Pegylated interferon-alfa
- Dabrafenib
- Tilmanocept
- Trametinib
- Pembrolizumab
- Nivolumab
- Talimogene laherparepvec
Why use immunologic approaches to treat melanoma?

The immune system has long been of interest to those treating Melanoma patients.

One of the first effective therapies was the non-specific Immune stimulant IL-2

Toxicity very severe
CR ~5%
Ipilimumab and nivolumab release the brakes on immune cells

It may be better to release the inhibition of the immune system rather than stimulate.
Getting T cells with Ipilimumab (Anti-CTLA4 body) Leads to Durable Response

Response ongoing years later with no new lesions

Weber J, Oncologist 2008;13(supp4):16
Ipilimumab (Anti-CTLA4) Improves Overall Survival in Stage IV Melanoma

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS Rate (95% CI): 21% (20–22%)
Pembrolizumab (Anti-PD1 Antibody) Leads To More Responses and Longer Progression-free Survival vs Ipilimumab

Hazard ratio for disease progression: 0.58
\( P < 0.001 \)

Pembrolizumab, Q2W
- 33% response rate

Ipilimumab
- 12% response rate

Robert et al, NEJM 2015;372:2521
Combining nivolumab and ipilimumab is better than ipilimumab alone.

But is it better than nivolumab alone????

Combining nivolumab and ipilimumab may be better than nivolumab alone.

- **Ipi-Nivo vs Ipi**  \[ P < 0.001 \]
- **Nivo vs Ipi**  \[ P < 0.001 \]

<table>
<thead>
<tr>
<th></th>
<th>Nivo+Ipi</th>
<th>Nivo</th>
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<tbody>
<tr>
<td>Response</td>
<td>57.6%</td>
<td>43.7%</td>
</tr>
<tr>
<td>mPFS</td>
<td>11.5 mos</td>
<td>6.9 mos</td>
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<tr>
<td>Survival</td>
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Combining nivolumab and ipilimumab is more efficacious than ipilimumab alone

As many Grade 3 or 4 AEs (54% vs 24%)

Six times as many Grade 3 or 4 AEs leading to treatment discontinuation (38% vs 13%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab plus ipilimumab (N=56)</th>
<th>Nivolumab (N=48)</th>
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<tbody>
<tr>
<td>Any treatment-related adverse event</td>
<td>56 (91)</td>
<td>43 (89)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 (75)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (34)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (15)</td>
<td>30 (63)</td>
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*Grade 3 or 4 adverse events that may lead to discontinuation of treatment.*
Can sequential treatment provide similar benefits with less toxicity?

Nivo → Ipi

Median change: -50.1%

Ipi → Nivo

Median change: +17.0%

Can sequential treatment provide similar benefits with less toxicity?
BRAF mutation status

- BRAF wild-type
- BRAF mutant

Treatment
d

- Dabrafenib alone
- Dabrafenib + trametinib

Survival analysis:

- Hazard ratio: 0.63 (95% CI, 0.42–0.94)
- P-value: 0.02

Latest OS estimation is >25 months

Long et al, NEJM 2014;371:1877
How to treat and when?

Speed of disease progression
- Need to be determined through sequential scans
- Plasma LDH levels
- Rapidly progressing brain mets

BRAF mutant melanoma patients may be better to get immunotherapy first

Still very much a work in progress
Example of Clinical Response to Adoptive Cell Therapy in Advanced Melanoma at the NCI
Rapid expansion starts after 30 million TIL are generated in plates; the process involves a fixed two week time period. 30-60 bags are required.

*TIL preparation cost = $52k ½ of cost due to IL-2
4 of 47 successful TIL expansions (94%)
0 treated with TIL of 47 resected patients (85%)
Median PFS 12 months; projected median OS is 52 months
3 of 36 (36%) patients have durable ongoing responses ranging from 16-55 months. Median follow up is 17 months.
Growing Network of TIL Therapy Centers

Moffitt, FL, MDACC, TX, MD
Uppsala, Sweden
Sheba, Israel
Copenhagen, DK
Lausanne, SUI
New Haven, CT
Manchester, UK

NKB, NL

Globally, clinical responses in ~50% of metastatic melanoma patients have been reported. Over 500 patients have been treated globally.
The Melanoma Revolution
Results of Phase III Trials in Metastatic Disease
Phase III Trial Results

DTIC:
PFS 1.6 months, OS 10 months

BRAFi+MEKi:
PFS 11 months, OS >25 months

Pembro:
PFS 5 months, OS >18 months

Ipi+Nivo:
PFS 11.5 months, OS ?

**Moffitt contributions to the melanoma revolution**

**Immune therapy**
Major contributor to all of the key trials on ipilimumab and nivolumab

First to demonstrate that patients tolerate nivolumab even following severe toxicity to ipilimumab

Conducted the first randomized trial comparing ipi>nivo and nivo>ipi which may ultimately become standard of care

**Targeted therapy**
Provided the preclinical rationale for BRAF-MEK inhibition

Accrued the most patients to the pivotal BRAF-MEK inhibitor trial

Initiating the first three agent targeted therapy trial for BRAF mutant
Ongoing Research in the Melanoma and Skin Cancers Research Center of Excellence

Melanoma signaling/genetics
- Smalley, PhD: Developing personalized therapy strategies for melanoma
- Chellappan, PhD: YAP-1 signaling in melanoma
- Koemen, PhD: Phosphoproteomic analysis of melanoma
- Yang, PhD: Mechanisms of melanoma cell signaling/metastasis
- Kim, PhD: Novel signaling pathways in melanoma (R-Ras and Ral-A)
- Rix, PhD: Using chemical proteomics to determine therapeutic targets in melanoma
- Mahajan, PhD: Wee1 as a novel therapeutic target in melanoma
- Morse, PhD: Targeted radiopharmaceuticals for melanoma
- Kanetsky, MPH, PhD: Melanoma metabolomics
- Forsyth, MD: Melanoma brain metastases and meningeal melanoma metastases
- Chen, PhD: Genetic analysis of melanoma
- Wan, PhD: Protein homeostasis in melanoma
- Karreth (starting May 2016): ceRNAs and melanoma development/progression

Melanoma immunology and tumor microenvironment
- Pilon-Thomas, PhD: Mechanisms of melanoma related T-cell suppression
- Mulé, PhD: Chemokine signatures/ectopic lymph nodes in melanoma
- Abate-Daga: CAR T-cells and melanoma
- Sarnaik, MD: Optimizing TIL therapy for melanoma
- Markowitz, MD: STAT1 nitrosylation and immune therapy escape
- Gillies, PhD: Hypoxia in the tumor microenvironment

Regional therapy
- Zager, MD: Regional intraarterial and intralesional therapy of skin and hepatic metastases

Non-melanoma skin cancer
- Rollison, PhD, MPH: Role of HPV in non-melanoma skin cancer development
- Tsai, MD, PhD (starting Aug 2016): miRNAs for the prevention of SCC
- Kim, MD, PhD: Radiation combined with immunotherapy in Merkel cell carcinoma