Approaches To Treating Advanced Melanoma

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Disclosures

- No relevant disclosures
Objectives

- Review mechanisms of targeted therapy and immunotherapy for melanoma
- Case based presentation
- Show the value of the dermatologist in advanced cases of melanoma
CASE

77yo woman who presented with a nodular melanoma, 3.5mm, non-ulcerated, MR 5, transected

Staging CT neck/C/A/P (-)

WLE showed residual 4.5mm, SLN was (-)

Stage IIB (pT4a, N0, M)

70% 5-year OS
Routine CT chest: metastatic melanoma

Next Steps?

- Consult thoracic oncology
- Radiation
- Hospice
- Systemic Immunotherapy

Began anti-PD1 therapy with pembrolizumab
Immunotherapy initiated with anti-PD1 therapy – *pembrolizumab*

After 12\textsuperscript{th} dose complete resolution

Side effects – all grade 1 (fatigue, weight loss, joint pain)
Spectacular Advances Evolving into Adjuvant

**Advanced Melanoma**

**Targeted therapies**
- Vemurafenib (Aug 2011)
- Trametinib (May 2013)
- Dabrafenib (May 2013)

**Combination Targeted Therapies**
- Dabrafenib + Trametinib (Jan 2014)
- Vemurafenib + Cobimetinib (Nov 2015)
- Encorafenib + Binimetinib (June 2018)

**Systemic Immunotherapies**
- Ipilimumab (March 2011)
- Pembrolizumab (Sept 2014)
- Nivolumab (Dec 2014)

**Combination Systemic Immunotherapies**
- Nivolumab + Ipilimumab (Oct 2015)

**Intralesional immunotherapy**
- Imlygic (Oct 2015)

**Adjuvant Therapy**
- PEG-IFN (Sept 2011)
- Ipilimumab (Oct 2015)
- Nivolumab (Dec 2017)
- Braf/Mek combination (April 2018)

2011 – 2018
15 FDA approvals
Melanoma Therapy: Broad Approaches

**Targeted Therapy**

- **Small molecule inhibitors**
  - Braf inhibitors
    - vemurafenib
    - dabrafenib
  - Mek inhibitors
    - trametinib
    - cobimetinib

**Checkpoint inhibitors**

- Ipilimumab (anti-CTLA4)
- Pembrolizumab (anti-PD1)
- Nivolumab (anti-PD1)
Clinical responses: targeted vs immunotherapy

Targeted

Immunotherapy

More survivors at beginning

More survivors at end - Tail of curve

Targeted therapies

Small molecule inhibitors: kinase inhibition

**BRAF-inhibitors**
- Vemurafenib
- Dabrafenib

**MEK-inhibitors**
- Trametinib
- Cobimetinib
Incidence of Key Driver Oncogenes in Melanoma

MAPK signaling pathway

- **BRAF** ~ 50%
- **NRAS** ~ 20%
- **CKIT** ~ 1%
  - Primarily mucosal and acral lentiginous
- **GNAQ/GNA11** ~ 1%
  - Almost exclusively uveal

Melanoma

RR: 50%
mPFS: 5~6 mo

RAF activation of the MAPK/ERK pathway

Oral inhibitors of BRAF kinases
1. Vemurafenib (Zelboraf®)
2. Dabrafenib (Tafinlar®)

BRAF - member of the RAF serine/threonine protein kinases
BRIM3 trial – Vemurafenib superior to Dacarbazine

OS: Brafi vs chemo 13.6mos vs 9.7mos
Phase III Study of Dabrafenib vs DTIC in Melanoma: Response and PFS

Most patients benefit from initial tumor shrinkage

PFS: Brafi vs chemo 6.9mos vs 2.7mos

Downstream targeting - MEK inhibition

RR: 22%
mPFS: ~ 5 mo

1st in class oral inhibitor MEK kinase

Trametinib (Mekinist®)

Melanoma
Phase III METRIC: Trametinib (MEKi) vs Dacarbazine or Paclitaxel


PFS: Trametinib vs chemo, 4.8 vs 1.5 mos

OS: Trametinib vs chemo, 81% vs 67% at 6 mos

HR: 0.45 (95% CI: 0.33-0.63; \( P < .001 \))

Trametinib (\( n = 214 \))

Chemotherapy (\( n = 108 \))

HR: 0.54 (95% CI: 0.32-0.92; \( P = .01 \))

Trametinib (\( n = 214 \))

Chemotherapy (\( n = 108 \))
Melanoma

**BRAFi + MEKi – Improved RR and PFS**

- **RR:** 65 ~ 75%
- **mPFS:** 10~12 mo

**Vemurafenib** (Zelboraf®) +
- **Cobimetinib** (Cotellic®)
- **Dabrafenib** (Tafinlar®) +
- **Trametinib** (Mekinist®)

Combining BRAF+MEK inhibitors decreases the incidence of cSCC

* 1 patient assigned to monotherapy received combination 150/2 and was included in the combination 150/2 safety analyses.
† No grade 4 adverse events reported for these categories.
‡ includes keratoacanthoma.

Immune *checkpoint* inhibitors

*anti-CTLA4*
Ipilimumab

*anti-PD1*
pembrolizumab, nivolumab
Ipilimumab: anti CTLA-4

Melanoma

Resting T cell

TCR
CD28
MHC
B7
Ipilimumab: anti CTLA-4

Melanoma

Activated T cell

Resting T cell

TCR
CD28
MHC
B7
Melanoma

Activated T cell

Resting T cell

TCR

CTLA4

MHC

B7

Ipilimumab: anti CTLA-4
Ipilimumab: anti CTLA-4

Melanoma

Resting T cell

TCR

CTLA4

MHC B7
Ipilimumab: anti CTLA-4

RR: ~10%
2yr OS: 20~ 25%
Recurrence ↓ by ~25%

Ipilimumab, gp100, or Both: OS in Advanced Melanoma

Median OS, Mos | HR | P Value
---|---|---
Ipilimumab + gp100 (n = 403) | 10.0 | 0.68 | < .001
Ipilimumab alone (n = 137) | 10.1 | 0.66 | .003
gp100 alone (n = 136) | 6.4 | --- | ---


2-yr OS:
- Ipi +/- gp100: ~23%
- Gp100 alone: 14%
Ipilimumab “survivors” have prolonged sustained response

Pooled analysis from 12 studies with 1,861 patients with metastatic melanoma

3-year OS ~ 20%

Curative potential

CTLA-4 Blockade Immune-Mediated Toxicities

Common (> 20%)
- Rash, pruritus
- Fevers, chills, lethargy
- GI: Diarrhea/colitis

Occasional (3% to 20%)
- Hepatitis/liver enzyme abnormalities
- Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency
- Vitiligo

Rare (< 2%)
- Episcleritis/uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

PD-1 Blockade

Release the brakes on pre-existing tumor reactive T cells

RR: 30% - 40%
1yr OS: 75%

Anti-PD-1 mAb (IgG4)
1. Pembrolizumab (Keytruda®)
2. Nivolumab (Opdivo®)

CD28/CTLA4 receptor family
### Pembrolizumab superior to ipilimumab (KEYNOTE 006)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab</th>
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<tbody>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>8.3 (6.5-11.2)</td>
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<tr>
<td>24 mos, %</td>
<td>34</td>
</tr>
<tr>
<td>33 mos, %</td>
<td>31</td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>32.3 (24.5-NR)</td>
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<tr>
<td>24 mos, %</td>
<td>55</td>
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<tr>
<td>33 mos, %</td>
<td>50</td>
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<tr>
<td>ORR, % (95% CI)</td>
<td>42 (38-46)</td>
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<tr>
<td>CR</td>
<td>13 (11-16)</td>
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<tr>
<td>PR</td>
<td>29 (25-33)</td>
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<tr>
<td>SD</td>
<td>21 (18-25)</td>
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<tr>
<td>PD</td>
<td>29 (26-33)</td>
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<tr>
<td>Median DoR, mos (range)</td>
<td>NR (1.0+ to 33.8+)</td>
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<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
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<tbody>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>3.3 (2.9-4.1)</td>
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<td>24 mos, %</td>
<td>15</td>
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<tr>
<td>33 mos, %</td>
<td>14</td>
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<tr>
<td>Median OS, mos (95% CI)</td>
<td>15.9 (13.3-22.0)</td>
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<td>24 mos, %</td>
<td>42</td>
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<tr>
<td>33 mos, %</td>
<td>39</td>
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<tr>
<td>ORR, % (95% CI)</td>
<td>16 (12-21)</td>
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<tr>
<td>CR</td>
<td>3 (1-6)</td>
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<td>SD</td>
<td>25 (20-31)</td>
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<tr>
<td>PD</td>
<td>39 (33-45)</td>
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<tr>
<td>Median DoR, mos (range)</td>
<td>NR (1.1+ to 34.8+)</td>
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</tbody>
</table>

HR (95% CI) 0.56 (0.47-0.67) for Pembrolizumab versus 0.70 (0.58-0.86) for Ipilimumab.
Nivolumab: OS Improved vs Dacarbazine in Untreated Melanoma With WT BRAF

*Checkmate-066*: randomized, double-blind phase III trial[1]

- **Nivolumab vs DTIC**
  - HR: 0.42[1]

- **Ipi/DTIC vs DTIC**
  - HR: 0.69[2]


**Pts Surviving (%)**
- Nivo: 1-yr OS: 73%
- Chemo: 1-yr OS: 42%

**Pts Who Died, n/N**
- Nivolumab: 50/210
- Dacarbazine: 96/208

**Median OS, Mos (95% CI)**
- Nivolumab: NR
- Dacarbazine: 10.8 (9.3-12.1)

**HR 0.42 (99.79% CI: 0.25-0.73; P < .001)**
Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

**Occasional (5% to 20%)**
- Fatigue
- Rash: maculopapular and pruritus
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis/liver enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

**Infrequent (< 5%)**
- **Pneumonitis**
- Grade 3/4 toxicities uncommon

Combination ipi (anti-CTLA4) + nivolumab (anti-PD1)

RR: ~60%

Melanoma

Activated T cell

Resting T cell

Tumor

Interferons

Ipilimumab (Yervoy®)

+ nivolumab (Opdivo®)

## CheckMate 067: Treatment-Related AEs

<table>
<thead>
<tr>
<th>Select Treatment-Related AEs, %</th>
<th>Nivo + Ipi (n = 313)</th>
<th>Nivo (n = 313)</th>
<th>Ipi (n = 311)</th>
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<tbody>
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<td>Grade 3/4</td>
<td>All Grades</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Maculopapular rash</td>
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<td>Diarrhea</td>
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<td>2</td>
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<tr>
<td>ALT increase</td>
<td>19</td>
<td>9</td>
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</tr>
<tr>
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<td>&lt;1</td>
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<tr>
<td>Pneumonitis</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

40% discontinue combo therapy
Talimogene laherparepvec: T-VEC
(Imlygic)

- Modified HSV-1
- Selective for cancer cells
- Tumor lysis
- Increase antigen presentation
- Produces GM-CSF

1st in-class intrallesional oncolytic immunotherapy
• median survival difference of 23 vs 19 months was observed with talimogene laherparepvec vs GM-CSF

hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.62, 1.00; $p = 0.051$

• Primary endpoint - durable response rate improved (16% vs 2%; T-VEC vs GM-CSF)
• 2/3 of injected lesions had an initial response
• 34% of non-injected non-visceral lesions
• 15% of visceral lesions
• Induces systemic antitumor responses
**Talimogene laherparepve: T-VEC (Imlygic)**

Durable RR: 16%

Tumor antigen

Activated T cell

Dendritic cell

Melanoma
Case Presentations