New Treatments for Metastatic Disease

Michael E Ming, MD, MSCE
Associate Professor of Dermatology
at the Hospital of the University of Pennsylvania
Philadelphia, PA
DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

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New Treatments for Metastatic Disease

I do not have any conflicts of interest.
Metastatic Melanoma

- Historically has a poor prognosis
  - Median survival around 6–9 months
  - 5-year survival <5%

- Prior to 2011, no FDA-approved therapy shown to prolong survival
Metastatic Melanoma

• Targeted therapy
  – Vemurafenib (BRAF inhibitor)
  – Dabrafenib (BRAF inhibitor)
  – Trametinib (MEK1/MEK2 inhibitor)
  – Combo of dabrafenib and trametinib
  – Combo of vemurafenib and cobimetinib

• Immunomodulator/checkpoint inhibitor
  – Ipilimumab (Ab against CTLA-4)
  – Nivolumab (PD-1 inhibitor)
  – Pembrolizumab (PD-1 inhibitor)
  – Combo of ipilimumab and nivolumab

• Talimogene laherparepvec
BRAF

- BRAF mutations in ~50% of melanomas
  - Of the BRAF mutations, 90% are V600E (some V600K)
  - Only FDA-approved against melanomas with V600E (V600K) mutations
BRAF inhibitor

vemurafenib

V600E mutation

Raf inhibitor
Vemurafenib

- Up to 80% will have at least partial response within weeks

- Many (?all) will have relapse
  - Median time to progression: 6 - 7 months
  - A very few long-term responders
Vemurafenib

- Toxic side effects
  - 40% needed dose reduction
  - Fatigue, arthralgia
  - Dermatologic manifestations
Vemurafenib and Keratoacanthoma/SCCs

• 20 - 30% develop KA-like SCCs
  – Wild-type BRAF in affected cells
Other targeted therapy

• DaBRAFenib
  – BRAF inhibitor
  – Similar response rate

• TraMEtinib/CobiMEtinib
  – MEK inhibitor
  – Side effect profile is different (cardiac)
Other targeted therapy

• BRAF/MEK combination therapy
  – Dabrafenib/Trametinib
  – Vemurafenib/Cobimetinib

  – Similar to each other
  – More effective than single-agent
Other targeted therapy

• BRAF/MEK combination therapy
  – Dabrafenib/Trametinib
  – Vemurafenib/Cobimetinib

Preference for targeted therapy is combination therapy (unless contraindicated)
Other targeted therapy

• BRAF/MEK combination therapy
  – Dabrafenib/Trametinib
  – Vemurafenib/Cobimetinib

Some early data indicate BRAF/MEK combo may lead to long-term response
Metastatic Melanoma

- Immunomodulator / Checkpoint inhibitor
  - Ipilimumab (Ab against CTLA-4)
  - Nivolumab (Ab against PD-1)
  - Pembrolizumab (Ab against PD-1)
- Combo of ipilimumab and nivolumab
Metastatic Melanoma

- Ipilimumab
- Nivolumab
- Pembrolizumab

MAB = monoclonal antibody
Ipilimumab

• 4 IV doses, 3 wks apart
  » Effect often towards end of dosing
    – 10 – 15% of patients will respond
    – But many (most?) will have durable response
Ipilimumab

- Toxic side effects
  - 34% stopped the drug
  - 2% died of drug side effects at higher dose
  - General activation of immune system
  - Immune-related issues
    » Diarrhea/colitis, hepatitis
    » Dermatologic manifestations
      • rash, pruritus
      • vitiligo
Nivolumab and Pembrozimulab

• IV, indefinitely (?)
• Higher response rate, faster
  – 30% will have objective response
• Fewer side effects
  – 10% d/c’d in pembro trials

• Principal advantage of ipi is Stage III resected disease (+SLN) indication
Ipilimumab/Nivolumab combo

• May have better response rate
  – 60%
  – Study not designed to see if better than nivo

• More side effects
  – 55% grade III/IV adverse events
    » Vs 16% for nivolumab alone
  – 43% had to stop
  – 27% did not get 4 cycles of drug
  – 3% of pts in original Phase II study died from drug

• Expensive
  – $300,000
Talimogene Laherparepvec

- Oncolytic virus
  - Modified HSV-1
- Inject directly into tumor
- Median 4 months
- No change in overall survival
Clinical decision making among approved agents

<table>
<thead>
<tr>
<th>Targeted Therapy (BRAF/MEK inh)</th>
<th>Immune Therapy (ipi or PD-1)</th>
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<tbody>
<tr>
<td>Only works w/V600E mut</td>
<td>Anyone</td>
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<tr>
<td>Higher Likelihood of Response</td>
<td></td>
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<tr>
<td>Shorter Time to Response</td>
<td></td>
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<tr>
<td>long-term benefit is unproven</td>
<td>Long-term response can occur</td>
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</tbody>
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*(courtesy Tara Gangadhar and Ravi Amaravadi)*
A young, previously healthy patient in the ICU from complications of a heavy tumor burden in the lungs, +V600E BRAF

1. Vemurafenib/Cobimetinib
   Dabrafenib/Trametinib
2. Nivolumab/pembrozimulab
3. Talimogene Laherparepvec
4. None of the above
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A young, otherwise healthy patient with a low tumor burden (but scattered) of metastatic disease, BRAF wild type

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Future directions

• Are results sustainable?
  – What happens when you take someone off immunotherapy?

• Biomarkers: who benefits?

• PD-L1 inhibitor

• Novel combos (simult or sequential)
Important

• Stage III pts approved for ipi

• Stage IIC (>4mm thick with ulceration) patients now in trials
Thank you for your attention!

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