Recent Advances in the Treatment and Management of Metastatic Melanoma

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Objectives

• Assess the efficacy and safety of currently available therapies in the treatment of metastatic melanoma

• Discuss the different types of immunotherapies available for the treatment of metastatic melanoma and their benefits versus targeted therapies

• Examine NCCN's latest guidelines on the treatment of metastatic melanoma

• Analyze strategies for managing the unique immune-related adverse events associated with the use of immunotherapy in patients with metastatic melanoma
I have no disclosures.

I will not discuss the unlabeled or unapproved use of a drug or product.

Melanoma: A Rising Threat

• In the Western world, the incidence of melanoma is increasing more rapidly than any other cancer.
• Lifetime risk of an individual American developing melanoma now near 1 in 70.

Currently Available Therapies

- Chemotherapy
  - dacarbazine, temozolomide, platinum, etc.
- Oncogenic pathway inhibitors
  - Selective BRAF inhibitors
- Immunotherapy
  - Ipilimumab, Interleukin-2

Efficacy & Safety: Chemotherapy

- DTIC (dacarbazine)
- Temozolomide (Temodar)
- Platinum/taxol

Response rates of 5-25%

Toxicities are familiar: nausea, vomiting, hair loss, fatigue, etc.
Efficacy & Safety: Chemotherapy

What I tell my patients:

• Standard chemotherapy is curative in some cancers (e.g. testicular, some lymphomas). In general, melanoma is not one of them.

• Chemo has a somewhat limited role in the treatment of this disease, usually for patients with a poor performance status or whose disease has progressed though other therapies.

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February 21, 2010:
BRAF inhibitor (vemurafenib)
Pathway Therapy

• Vemurafenib (Zelboraf) was FDA approved in August 2011 for metastatic melanoma harboring a BRAF V600E mutation
• The name "vemurafenib" comes from V600E mutated BRAF.

Efficacy & Safety: Vemurafenib

• BRIM-3 trial: phase 3 randomized clinical trial comparing vemurafenib with dacarbazine in 675 patients with untreated, metastatic V600E mutant melanoma

• Overall response rate:
  – 48.4% vemurafenib
  – 5.5% dacarbazine

Chapman et al, NEJM, 2011
Efficacy & Safety: Vemurafenib

• Side effects:
  – Arthralgia, rash, fatigue, alopecia
  – Keratoacanthoma or squamous cell carcinoma
  – Photosensitivity
  – Nausea, diarrhea
  – BRIM-3 trial: 38% of patients required dose modification because of side effects.

Vemurafenib

• What I tell my patients:
  – Therapy often works quickly and effectively; good for patients who need an immediate response
  – In general, responses are not durable: resistance often develops after 6-8 months
Currently Available Therapies

- Chemotherapy
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- Oncogenic pathway inhibitors
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- Immunotherapy
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Why Immunotherapy?

- Melanoma is perhaps the most immunogenic human cancer
- Human immune system can attack with virtually unlimited precision
- Unlike targeted therapy, can adapt to ongoing tumor mutations and avoid drug resistance
- Responses are often durable (immune memory)
  - e.g. lifelong protection against measles after vaccination
**Efficacy & Safety: Interleukin-2**

- Administered in ICU; ~100 centers in U.S.
- Approximately 15-20% response rate
- 5% long-term responders (cure?)

- Side effects: Hypotension, tachycardia, capillary leak syndrome, altered mental status

**Efficacy & Safety: Ipilimumab**

- 2011: Ipilimumab (Yervoy, anti-CTLA-4) was FDA-approved for the treatment of metastatic melanoma after a 676-patient randomized study demonstrated improved overall survival.
Survival: Ipilimumab

Efficacy and Safety: Ipilimumab

- Serious (grade 3-4) drug-related adverse events occurred in 17-23% of patients, with a 2% mortality rate.
- Immune-related Adverse Events:
  - Colitis (diarrhea, abd pain, blood in stool)
  - Hepatitis (jaundice, LFT rise)
  - Dermatitis (pruritus, rash, rare TEN)
  - Hypophysitis (headache, endocrine dysfunction)
  - Nephritis (creatinine rise)
  - Neuropathies (numbness, weakness, paresthesias)
  - Others

Adapted from Hodi et al. NEJM 2010
Understanding irAEs: Immune Checkpoints

Kinetics of appearance of immune-related adverse event.

Adapted from Sharpe et al., Nat Rev 2002


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Management of Immune-related Adverse Events (irAEs)

- irAEs are diagnosed by exclusion: rule out other etiologies (e.g. infection, neoplasm, metabolic causes, effects of other drugs)
- Management for most irAEs based on severity
- In general:
  - grade 1-2: supportive care; +/- withhold ipilimumab
  - grade 3-4: corticosteroids; discontinue ipilimumab

irAE Management Example: Colitis

- **Severe enterocolitis**
  - Permanently discontinue ipilimumab
  - Systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent); infliximab if refractory
  - Upon improvement to ≤ grade 1, taper steroids over ~4 weeks

- **Moderate enterocolitis**
  - Withhold ipilimumab, administer anti-diarrheal Rx
  - If moderate enterocolitis persists for > 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent
irAE Management Example: Colitis

• For patients with complete or partial resolution of adverse reactions (Grade 0-1) who are receiving less than 7.5 mg/day prednisone or equivalent, resume ipilimumab every 3 weeks until administration of all 4 planned doses or 16 weeks from first dose, whichever occurs first.
Looking forward: Pathway Blockade

• Dabrafenib (BRAF inhib.) plus Trametinib (MEK inhib.)
  – Median progression-free survival in the combination group (BRAF+MEK) was 9.4 months, as compared with 5.8 months in the monotherapy group (BRAF alone)

Flaherty et al, NEJM, 2012
Looking forward: Immunotherapy

Adapted from Sharpe et al., Nat Rev 2002

Clinical activity of anti-PD-1 (nivolumab/BMS-936558)

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<th>Tumor Type</th>
<th>Dose (mg/kg)</th>
<th>No. pts</th>
<th>ORR (CR/PR) No. pts (%)</th>
<th>SD ≥24 wk No. pts (%)</th>
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<td>10 (29)</td>
<td>9 (27)</td>
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</tbody>
</table>

In patients with ≥1 year follow-up, 28/54 (52%) of responses lasted ≥1 year

Topalian et al., ESMO 2012
Questions?