Major Changes in Systemic Therapy for Advanced Melanoma

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Featuring:

- Updates on immune checkpoint therapies and new targeted therapies
- FDA approval for combination ipilimumab + nivolumab
- FDA approval for high-dose ipilimumab for resected, high-risk melanoma
- FDA approval for talimogene laherparepvec (T-VEC)
- FDA approval for cobimetinib in combination with vemurafenib
Case Study

• **2013:** 45-year-old man – “mole” on the midback became pruritic, bled
  – Biopsy: melanoma, 3.5 mm depth, ulcerated, mitotic index 4/mm²
  – Wide local excision and sentinel node biopsy of right axilla: 2 sentinel nodes + Completion node dissection: 12 nodes negative
  – Staging: T4B N2A M0

• **Jan 2015:** patient noticed two lumps under skin between wide local excision site and axilla.
  – Core biopsy: Positive for melanoma
  – Molecular assay: Positive for BRAF V600E mutation
  – Imaging: bilateral lung nodules (new) and subcentimeter, but new liver lesion. Brain MRI negative.
  – Performance status 0; LDH within normal limits; mild hypertension on lisinopril, but no other medical problems

LDH, lactate dehydrogenase
What is the best treatment option?

1. Pembrolizumab (anti-PD-1) monotherapy
2. Dabrafenib + trametinib targeted therapy
3. High-dose interleukin-2 (IL-2)
4. Anti-CTLA-4 (ipilimumab) + nivolumab (anti-PD-1) combination immunotherapy
5. Intratumoral T-VEC

Melanoma

Systemic therapy for metastatic or unresectable disease

First-line therapy
- Immunotherapy
  - Anti PD-1 monotherapy
    - Pembrolizumab
    - Nivolumab (category 1)
  - Targeted therapy if BRAF mutated; preferred if clinically needed for early response
    - Combination therapy (preferred)
      - Dabrafenib/trametinib (category 1)
      - Vemurafenib/cobimetinib (category 1)
    - Single agent therapy
      - Vemurafenib (category 1)
      - Dabrafenib (category 1)
  - Clinical trial

Second-line or subsequent therapy
- Anti PD-1 monotherapy
  - Pembrolizumab
  - Nivolumab
  - Nivolumab/ipilimumab
  - Ipilimumab (category 1)
  - Targeted therapy if BRAF mutated
    - Combination therapy (preferred)
      - Dabrafenib/trametinib
      - Vemurafenib/cobimetinib
    - Single agent therapy
      - Vemurafenib
      - Dabrafenib
    - High-dose IL-2
    - Biochemotherapy (category 28)
    - Cytotoxic agents
    - Imatinib for tumors with activating mutations of C-KIT
    - Clinical trial

Disease progression or maximum clinical benefit from BRAF targeted therapy

Performance status (PS)
- 0-2
- 3-4

Consider best supportive care (See NCCN Guidelines for Palliative Care)
Ipilimumab: Mechanism of Action

**T-cell activation**
- T cell
- TCR
- CD28
- B7
- APC
- MHC

**T-cell inhibition**
- T cell
- TCR
- CD28
- CTLA-4
- B7
- APC
- MHC

**T-cell potentiation**
- T cell
- TCR
- CD28
- B7
- APC
- MHC

**CTLA-4** blocks

**APC**, antigen-presenting cell; **MHC**, major histocompatibility complex; **TCR**, T-cell receptor

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Ipilimumab Registration Trials

- **Second Line MDX010-20 Trial in HLA-A2 Positive Disease (N=650)**
  - 3 arms 3:1:1 (ipilimumab + gp100 vaccine, ipilimumab alone, gp100 alone)
  - 1st study in metastatic melanoma to demonstrate OS benefit in large randomized placebo-controlled trial

- **First Line CA184-024 Trial, Randomized Placebo Control (N=500)**
  - Ipilimumab + DTIC vs Placebo + DTIC
  - OS advantage for Ipilimumab + DTIC versus Placebo + DTIC

DTIC, dacarbazine; gp100, glycoprotein 100 peptide vaccine.
Overall Survival

Comparison     HR     p-value
Arms A vs. C  0.68     0.0004
Arms B vs. C  0.66     0.0026


Pooled Analysis of Long-term Survival Data from Phase II and III Trials of Ipilimumab in Unresectable or Metastatic Melanoma
Immune-related Adverse Events (irAEs) Associated with Ipilimumab

Skin:
- Pruritus
- Rash

Gastrointestinal
- Diarrhea
- Abdominal Pain
- Blood in stool
- Bowel perforation
- Peritoneal signs

Liver
- ↑ AST/ALT, Bilirubin

Endocrine
- Fatigue
- Headache
- Mental status changes
- Hypotension
- Abnormal thyroid function tests/serum chemistries

Neurological
- Uni- or bilateral weakness
- Sensory alterations
- Paresthesias

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Immune-related Adverse Events (irAEs) Associated with Ipilimumab**

**Management of Gastrointestinal irAEs**

*Mild toxicity:* Evaluate for other causes of symptoms

Symptomatic therapy

*Moderate toxicity:* 4-6 stools/day over baseline, abdominal pain, blood in stool

- Withhold ipilimumab
- Consider anti-diarrheal medication/nutritional modification
- If symptoms persist >1 week, prednisone at 0.5 mg/kg/day or equivalent

*Severe toxicity:* ≥7 stools/day over baseline, peritoneal signs consistent with perforation, ileus, fever

- Discontinue ipilimumab
- Evaluate for bowel perforation
- Consider endoscopy
- Steroids at 1-2 mg/kg/day (of prednisone or equivalent) until improvement, then taper over a month


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**Therapeutic Biology of Melanoma**


MHC, major histocompatibility complex; TCR, T-cell receptor
Activity of Anti–Programmed Death 1 (PD-1) Antibody (Nivolumab) in Patients with Refractory Melanoma

Complete/partial Response (CR/PR): 33/107 (31%)
Stable Disease (SD): 7/107 (7%)


Anti-PD-1 (Pembrolizumab) in Ipilimumab-refractory Melanoma

- 173 patients with melanoma that progressed after ≥2 doses of ipilimumab
- Allocated randomly to pembrolizumab IV every 3 weeks at 2 or 10 mg/kg
- With both doses: Safety profile similar
  ORR 26%

FDA approved pembrolizumab for: unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf
Pembrolizumab (anti-PD-1) in Ipilimumab-refractory Advanced Melanoma: a Randomised Dose-comparison Cohort of a Phase 1 Trial

Adverse Reactions in >10% of Patients Treated with 2 mg/kg Anti-PD-1 (Pembrolizumab)

<table>
<thead>
<tr>
<th></th>
<th>All grade (%)</th>
<th>Grade 3 (%)</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>47</td>
<td>7</td>
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<tr>
<td>Peripheral edema</td>
<td>17</td>
<td>1</td>
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<tr>
<td>Chills</td>
<td>14</td>
<td>0</td>
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<tr>
<td>Nausea</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
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<td>Diarrhea</td>
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<td>Vomiting</td>
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<td>0</td>
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<tr>
<td>Cough</td>
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<td>1</td>
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<tr>
<td>Dyspnea</td>
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<td>2</td>
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<tr>
<td>Pruritus</td>
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<td>0</td>
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<td>Rash</td>
<td>29</td>
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<tr>
<td>Vitiligo</td>
<td>11</td>
<td>0</td>
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<tr>
<td>Arthralgia</td>
<td>20</td>
<td>0</td>
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<tr>
<td>Myalgia</td>
<td>14</td>
<td>1</td>
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<tr>
<td>Headache</td>
<td>15</td>
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<tr>
<td>Anemia</td>
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<td>5</td>
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<tr>
<td>Insomnia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

There were no Grade 5 AEs reported. Of the >10% AEs, none were reported as Grade 4.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf

Nivolumab in Previously Untreated Melanoma Without BRAF Mutation

418 patients with metastatic melanoma

Previously untreated, BRAF mutation negative, Performance Score 0-1

Randomly assigned to:

- Nivolumab 3 mg/kg every two weeks and dacarbazine-matched placebo every 3 weeks (N = 210)
- Dacarbazine 1000 mg/m² every three weeks and nivolumab-matched placebo every 2 weeks (N = 208)

Nivolumab objective response rate = 40%

Dacarbazine objective response rate = 14%

Tumor Staining for PD-L1: Correlation with Response to Therapy with Anti-PD-1 or Anti-PD-L1

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th>PD-L1 Positive</th>
<th>PD-L1 Negative</th>
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<tbody>
<tr>
<td>Topalian (NEJM 2012)</td>
<td>9/25</td>
<td>0/17</td>
</tr>
<tr>
<td>Grosso (ASCO 2013)</td>
<td>7/16</td>
<td>3/18</td>
</tr>
<tr>
<td>Herbst (ASCO 2013)</td>
<td>13/33</td>
<td>8/61</td>
</tr>
<tr>
<td>Robert (NEJM 2015)</td>
<td>53%</td>
<td>33%*</td>
</tr>
</tbody>
</table>

*PD-L1 negative or indeterminate

CA209-067 Study Design

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone

- Unresectable or Metastatic Melanoma
  - Previously untreated
  - 945 patients

Randomize 1:1:1

N=314

- NIVO 1 mg/kg Q2W + IPI-matched placebo
- NIVO 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

- NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

- IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression** or unacceptable toxicity

- Stratify by:
  - PD-L1 expression*
  - BRAF status
  - AJCC M stage

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

AJCC, American Joint Committee on Cancer; IPI, ipilimumab; NIVO, nivolumab; Q2W, every 2 weeks; Q3W, every 3 weeks.

CA209-067 Co-primary Endpoint: Progression-Free Survival (Intent-to-Treat)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n=314)</th>
<th>NIVO (n=316)</th>
<th>IPI (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9</td>
<td>2.9</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank \(P<0.00001\) vs. IPI
**Exploratory endpoint

IPI, ipilimumab; NIVO, nivolumab.

CA209-067 Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n=314)</th>
<th>NIVO (n=316)</th>
<th>IPI (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)*</td>
<td>57.6 (52.0–63.2)</td>
<td>43.7 (38.1–49.3)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td>Two-sided (P) value vs IPI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>Best overall response — %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>11.5</td>
<td>8.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>46.2</td>
<td>34.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.1</td>
<td>10.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22.6</td>
<td>37.7</td>
<td>48.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Duration of response (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR (13.1, NR)</td>
<td>NR (11.7, NR)</td>
<td>NR (6.9, NR)</td>
</tr>
</tbody>
</table>

*By RECIST v1.1.

IPI, ipilimumab; NIVO, nivolumab; NR, not reached; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors.
CA209-067 Tumor Burden Change From Baseline

NIVO + IPI
Median change: -51.9%

NIVO
Median change: -34.5%

IPI
Median change: +5.9%

CA209-067 Conclusions

- NIVO alone and NIVO + IPI significantly improved PFS and ORR vs. IPI alone in patients with previously untreated melanoma
  - NIVO + IPI resulted in numerically longer PFS and a higher ORR vs. NIVO alone
  - In patients whose tumors have ≥5% PD-L1 expression, both NIVO alone and NIVO + IPI resulted in a similar prolongation in PFS, although ORR was numerically higher with NIVO + IPI
- Based upon available evidence, the combination represents a means to improve outcomes vs. NIVO alone, particularly for patients whose tumors have <5% PD-L1 expression

IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; ORR, objective response rate.
Overall Survival of Patients Receiving Cell Transfer Based on Prior Treatment Received


Figure 1 from Naidoo, J. British Journal of Cancer. 2014. Advance Online Publication doi:10.1038/bjc.2014.348
**EORTC 18071/CA184-029: Study Design**

Iplimumab vs Placebo after Complete Resection of Stage III Melanoma  
LBA 9008, presented by Alexander Eggermont at 2014 ASCO Annual Meeting

- **N=951**
  - High-risk stage III, completely resected melanoma

- **N=475**
  - **INDUCTION**
    - Iplimumab 10 mg/kg Q3W X4
  - **MAINTENANCE**
    - Iplimumab 10 mg/kg Q12W up to 3 years

- **N=476**
  - **INDUCTION**
    - Placebo Q3W X4
  - **MAINTENANCE**
    - Placebo Q12W up to 3 years

Treatment up to a maximum 3 years, or until disease progression, intolerable toxicity, or withdrawal

**Stratification factors:**
- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC 4+ positive lymph nodes)
- Regions (North America, European countries and Australia)

Primary Endpoint: Recurrence-free Survival (IRC)

Presented By Alexander Eggermont at 2014 ASCO Annual Meeting

Deaths Related to Study Drug

- Five patients (1.1%) died due to drug-related AEs in the ipilimumab group:
  - Three patients with colitis (2 with gastrointestinal perforations)
  - One patient with myocarditis
  - One patient with Guillain-Barré syndrome
- No deaths related to study drug were reported in the placebo group

Presented By Alexander Eggermont at 2014 ASCO Annual Meeting
**ECOG 1609: Phase III Trial of Ipilimumab Versus Interferon for Resected, High-risk Melanoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Resected</th>
<th>Induction</th>
<th>Maintenance</th>
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</thead>
<tbody>
<tr>
<td>III-B</td>
<td></td>
<td>Ipilimumab 10 mg/kg Every 3 weeks x 4 doses</td>
<td>Ipilimumab 10 mg/kg weeks 24, 36, 48, 60</td>
</tr>
<tr>
<td>III-C</td>
<td></td>
<td>Ipilimumab 3 mg/kg Every 3 weeks x 4 doses</td>
<td>Ipilimumab 3 mg/kg weeks 24, 36, 48, 60</td>
</tr>
<tr>
<td>IV-M1a</td>
<td></td>
<td>Interferon α2b 20 MU/m²/d IV Mon-Fri for 4 weeks</td>
<td>Interferon α2b 10 MU/m²/day SC 3x/week for 48 weeks</td>
</tr>
<tr>
<td>M1b</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

~ 1500 patients

[https://clinicaltrials.gov/ct2/show/record/NCT01274338](https://clinicaltrials.gov/ct2/show/record/NCT01274338)

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**Case Study**

- **2010:** 50-year-old man – melanoma excised left calf, 0.66 mm depth, no ulceration. Staging T1Ac N0 M0.

- **Fall 2015:** Patient noticed fullness left groin. Fine-needle aspiration biopsy: positive for melanoma. Left inguinal lymph node dissection: 9 nodes, 3 positive for melanoma, largest 3.5 cm without extracapsular extension. Staging workup including PET/CT: negative.

- Staging T1 N2B M0, stage IIIB.
Case Study (cont)

- Ipilimumab (10 mg/kg) adjuvant therapy started. Eight days after the first dose, patient developed red rash, intensely pruritic.

- Topical potent steroid cream and antihistaminics administered. Rash gradually subsided but the day 22 dose was skipped. The patient received another dose of ipilimumab on day 42.

- Six days later, the patient had abrupt onset eye pain, hyphema. A diagnosis of anterior uveitis was made and prednisone 1 mg/kg/day started. Eye pathology worsened, with edema of extraocular muscles (myositis) causing proptosis and increased intraocular pressure.

- Infliximab 5 mg/kg administered with rapid reduction in pain, intraocular pressure. Gradual taper of prednisone (5 mg reduction every 5 days).

What is the best treatment option?

1. Pembrolizumab (anti-PD-1) monotherapy
2. Dabrafenib + trametinib targeted therapy
3. High-dose interleukin-2 (IL-2)
4. Anti-CTLA-4 (ipilimumab) + nivolumab (anti-PD-1) combination immunotherapy
5. Intratumoral T-VEC

Audience Polling Results

- Pembrolizumab (anti-PD-1) monotherapy: 36%
- Dabrafenib + trametinib targeted therapy: 21%
- High-dose interleukin-2 (IL-2): 4%
- Anti-CTLA-4 (ipilimumab) + nivolumab (anti-PD-1) combination immunotherapy: 38%
- Intratumoral T-VEC: 1%
**HIGH-DOSE IPILIMUMAB**

6Adjuvant ipilimumab is associated with improvement in recurrence-free survival. Its impact on overall survival has not been reported. The recommended dose of ipilimumab (10 mg/kg) was associated with adverse events which led to the discontinuation of treatment in 52% of patients. There was a 1% drug-related mortality rate.

7The clinical trial excluded patients with sentinel lymph node metastases ≤1 mm in size and who did not undergo CLND. The decision to use ipilimumab should be based on risk of recurrence balanced against the risk of treatment-related toxicity. It is unclear whether the decision should be based on CLND.
Talimogene Laherparepvec (T-VEC) Improves Durable Response Rate in Patients with Advanced Melanoma

Patients with injectable melanoma that was not surgically resectable (N=436) randomized to:
- T-VEC (n=295) intralesional injection week 0, 3, then every 2 weeks
- GM-CSF (n=141) 125 mcg/m² SC days 1-14 every 28 days

<table>
<thead>
<tr>
<th></th>
<th>T-VEC (n=295)</th>
<th>GM-CSF (n=141)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable Response</td>
<td>48 (16%)</td>
<td>3 (2.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CR</td>
<td>32 (10.8%)</td>
<td>1 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>46 (15.6%)</td>
<td>7 (5%)</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>26.4%</td>
<td>5.7%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

GM-CSF, granulocyte macrophage colony-stimulating factor.

Antitumor Activity of Talimogene Laherparepvec (T-VEC)

Primary Analysis of Overall Survival (OS) in Intent-to-treat Population

GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, Talimogene Laherparepvec

IIIB, IIIC, IVM1a

IV M1b or IV M1c

First-line therapy

≥2nd Line

Outcomes in Patient Subgroups

GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, Talimogene Laherparepvec
Kinase Signaling Pathways in Melanoma


Melanoma

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

FIRST-LINE THERAPY
- Immunotherapy
  - Anti PD-1 monotherapy
  - Pembroliuzumab
  - Nivolumab
  - Nivolumab/ipilimumab (category 1)
- Targeted therapy if BRAF mutated; preferred if clinically needed for early response
- Combination therapy (preferred)
  - Dabrafenib/trametinib (category 1)
  - Vemurafenib/cobimetinib (category 1)
  - Single agent therapy
    - Vemurafenib (category 1)
    - Dabrafenib (category 1)
  - Clinical trial

PERFORMANCE STATUS (PS)

SECOND-LINE OR SUBSEQUENT THERAPY
- Anti PD-1 monotherapy
  - Pembroliuzumab
  - Nivolumab
  - Nivolumab/ipilimumab
  - Ipilimumab (category 1)
- Targeted therapy if BRAF mutated
  - Combination therapy (preferred)
    - Dabrafenib/trametinib
    - Vemurafenib/cobimetinib
  - Single agent therapy
    - Vemurafenib
    - Dabrafenib
  - High-dose IL-2
  - Biochemotherapy (category 28)
  - Cytotoxic agents
  - Imatinib for tumors with activating mutations of C-KIT
  - Clinical trial

Consider best supportive care (See NCCN Guidelines for Palliative Care)

Metastatic or unresectable disease
**Phase III trial of Vemurafenib Versus Dacarbazine in Metastatic Melanoma**

Previously untreated patients with metastatic melanoma

2107 patients screened; 675 patients randomized

Vemurafenib (n = 337) vs. Dacarbazine (n = 338)

960 mg oral BID vs. 1000 mg/m² every 3 weeks

PET Scans at Baseline and Day 15 After Vemurafenib


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Adverse Events in 618 Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vemurafenib (N=316)</th>
<th>Dacarbazine (N=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>60 (18)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>13 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>33 (10)</td>
<td>0</td>
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<tr>
<td>Grade 3</td>
<td>28 (18)</td>
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<tr>
<td>Fatigue</td>
<td>36 (11)</td>
<td>13 (12)</td>
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<tr>
<td>Grade 3</td>
<td>6 (2)</td>
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<tr>
<td>Cutaneous squamous-cell carcinoma</td>
<td>40 (12)</td>
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<td>Grade 3</td>
<td>7 (2)</td>
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<tr>
<td>Keratoacanthoma</td>
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<td>0</td>
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<tr>
<td>Grade 2</td>
<td>25 (7)</td>
<td>32 (11)</td>
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<tr>
<td>Grade 3</td>
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<td>5 (2)</td>
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<tr>
<td>Alopecia</td>
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<tr>
<td>Grade 2</td>
<td>19 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vemurafenib (N=316)</th>
<th>Dacarbazine (N=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkeratosis</td>
<td>17 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Diarhoea</td>
<td>16 (5)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (4)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (3)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (1)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Verrucal Keratosis


Well-differentiated Squamous Cell Carcinomas

Keratosis Pilaris-like Reaction

Hyperkeratotic Hand-foot Reaction

Dabrafenib in BRAF-mutated Metastatic Melanoma

733 patients enrolled; 250 randomized

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR (n)</th>
<th>PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib 150 mg oral BID (n=187)</td>
<td>6 (3%)</td>
<td>87 (47%)</td>
</tr>
<tr>
<td>Dacarbazine 1000 mg/m² IV every 3 weeks (n=63)</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

Progression-free Survival

**COMBI-d: Study Design**

- **Primary Endpoint** = Investigator-assessed PFS
- **Secondary Endpoints** = Overall Survival, Overall Response Rate, Duration of Response
- **Safety**

- BRAF V600E/K
- Unresectable stage IIIC/IV
- Treatment naïve
- ECOG PS 0/1
- No brain mets, unless
  - Treated
  - Stable > 12 wks

**Stratification**
- BRAF mut V600E v K
- LDH (>ULN v ≤ ULN)

**Presented By Georgina Long at 2014 ASCO Annual Meeting**

---

**A**

![Graph showing progression-free survival](image)

Dabrafenib + Trametinib (n=211) vs Dabrafenib (n=212)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Dabrafenib + Trametinib (n=211)</th>
<th>Dabrafenib (n=212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>11.0</td>
<td>8.8</td>
<td>0.0004</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>25.1</td>
<td>18.7</td>
<td>0.0107</td>
</tr>
<tr>
<td>2-year OS</td>
<td>51%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>16%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>53%</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

After cessation of study treatment, 33% of patients in the dabrafenib/trametinib arm and 51% of patients in the dabrafenib arm received other treatments, most commonly ipilimumab.

In the dabrafenib/trametinib group, fever and flu-like reaction were more common, but cutaneous squamous cell cancers and hyperkeratosis were less common.
Pyrexia: Temp ≥ 38.5°C is common (~55%) with combined dabrafenib and trametinib (less frequent with BRAF monotherapy ~20%).

Onset often 2-4 weeks following the start of therapy

May be associated with chills, night sweats, rash, dehydration, electrolyte abnormalities, and blood pressure. Stopping dabrafenib at the onset of pyrexia will often interrupt the episode, and treatment can be resumed with full-dose dabrafenib upon resolution of pyrexia and pyrexia-related symptoms.

Upon re-exposure to dabrafenib, pyrexia events may recur, but grade >3 events are uncommon (21%).

For prolonged or severe pyrexia not responsive to discontinuation of dabrafenib, prednisone (10 mg/day) may be used. Patients with pyrexia should be advised to use antipyretics as needed and increase fluid intake.

Overall Survival and Durable Responses with Dabrafenib + Trametinib

• A Phase I/II study of dabrafenib and trametinib contained four parts (A, B, C, D).
• This analysis includes patients who were BRAF inhibitor naïve and received dabrafenib 150 mg BID + trametinib 2 mg/day.

- Baseline prognostic features for good outcome: normal LDH, fewer metastases
- Normal baseline LDH and CR associated with 3-year OS rate >60%

LDH, lactate dehydrogenase level.
coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in BRAF^{V600E/M}-Mutated Metastatic Melanoma: Trial Overview

**Primary endpoint**
- Investigator-assessed PFS per RECIST v1.1

**Secondary endpoints**
- OS, ORR per RECIST v1.1, DOR, IRC-assessed PFS, and safety

DOR, duration of response; IRC, independent review committee; PS, performance score; R, randomized; RECIST, response evaluation criteria in solid tumours.


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coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in BRAF^{V600E/M}-Mutated Metastatic Melanoma: Investigator-Assessed PFS in the ITT Population (01/16/15 Cutoff)†

![Graph showing Investigator-Assessed PFS in the ITT Population](image)

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib + Placebo</th>
<th>Vemurafenib + Cobimetinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>180 (72.8)</td>
<td>145 (57.5)</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>7.20 (2.50-7.49)</td>
<td>12.25 (9.80-13.37)</td>
</tr>
<tr>
<td>Stratified hazard ratio (95% CI)</td>
<td>0.58 (0.46-0.719)</td>
<td></td>
</tr>
</tbody>
</table>

### coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in BRAFV600E-Mutated Metastatic Melanoma: Best Confirmed Response Rate and Duration of Response (01/16/15 Cutoff)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib + Placebo ((n = 248))</th>
<th>Vemurafenib + Cobimetinib ((n = 247))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective confirmed response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with objective response, n (%)</td>
<td>124 (50.0) (43.61-56.36)</td>
<td>172 (68.6) (63.49-73.31)</td>
</tr>
<tr>
<td>Difference in objective response rates (95% CI)</td>
<td>19.64 (10.03-29.25)</td>
<td></td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>26 (10.5)</td>
<td>39 (15.8)</td>
</tr>
<tr>
<td>Partial response</td>
<td>98 (39.5)</td>
<td>133 (53.3)</td>
</tr>
<tr>
<td>Duration of response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with an event, n (%)</td>
<td>73 (28.9)</td>
<td>84 (48.8)</td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td>9.23 (6.52-12.76)</td>
<td>12.98 (11.10-16.62)</td>
</tr>
<tr>
<td>Range, months</td>
<td>1.77-17.88</td>
<td>2.86-23.11</td>
</tr>
</tbody>
</table>


### coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in BRAFV600E-Mutated Metastatic Melanoma: Final OS (08/28/15 Cutoff)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib + Placebo ((n = 248))</th>
<th>Vemurafenib + Cobimetinib ((n = 247))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>141 (56.9)</td>
<td>114 (45.2)</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>17.4 (13.9-19.5)</td>
<td>23.3 (20.3-26.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI) (P) value</td>
<td>0.70 (0.55-0.89)</td>
<td>0.000</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>10.5</td>
<td></td>
</tr>
</tbody>
</table>

Atkinson, V. Presented at 2015 Society for Melanoma Research.
Toxicities of Vemurafenib + Cobimetinib

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rate</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous malignancies</td>
<td>6% cSCC or keratoacanthoma, 4.5% bcc, 0.8% second primary melanoma</td>
<td>Dermatological exam at baseline and every 2 months</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>13% all grades, 1.2% grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>26% grade 2-3 decrease in LVEF; safety not established for LVEF &lt;50%</td>
<td></td>
</tr>
<tr>
<td>Serous retinopathy</td>
<td>26% all grades</td>
<td>Ophthalmological exam at regular intervals and for new/worse visual disturbances</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>Grade 3-4: ALT 11%, AST 7%, bilirubin 1.6%, ALP 7%</td>
<td>Monitor LFTs monthly</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>12% grade 3-4 CPK elevations</td>
<td>Serum CPK and creatinine levels at baseline, then periodically during therapy</td>
</tr>
<tr>
<td>Rash</td>
<td>16% grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>47% all grades, 4% grade 3</td>
<td></td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bcc, basal cell carcinoma; CPK, creatinine phospho kinase; cSCC, cutaneous squamous cell carcinoma; LFTs, liver function tests; LVEF, left ventricular ejection fraction.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206192s000lbl.pdf
Effects of Immunotherapy and Targeted Therapy on Melanoma Survival Curves


NCCN Recommendations for Metastatic or Unresectable Melanoma: First-line Systemic Therapy

<table>
<thead>
<tr>
<th>BRAF Mutated</th>
<th>BRAF Wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred if need early response</td>
<td></td>
</tr>
<tr>
<td>• BRAF/MEK inhibitor combination (preferred):</td>
<td>• Anti-PD-1 monotherapy (nivolumab or pembrolizumab)</td>
</tr>
<tr>
<td>▪ Dabrafenib/trametinib</td>
<td>▪ Ipilimumab/nivolumab combination</td>
</tr>
<tr>
<td>▪ Vemurafenib/cobimetinib</td>
<td>▪ Clinical trial</td>
</tr>
<tr>
<td>▪ BRAF inhibitor monotherapy (vemurafenib or dabrafenib)</td>
<td></td>
</tr>
<tr>
<td>All other cases</td>
<td></td>
</tr>
<tr>
<td>• Anti-PD-1 monotherapy (nivolumab or pembrolizumab)</td>
<td></td>
</tr>
<tr>
<td>• Ipilimumab/nivolumab combination</td>
<td></td>
</tr>
<tr>
<td>• Clinical trial</td>
<td></td>
</tr>
</tbody>
</table>
### Unanswered questions:

- Optimal duration of therapy?
- Biomarkers to predict response?
- Combination vs sequential therapy?
- Role of T-cell therapies?
Thank You

John A. Thompson, MD
jat@uw.edu