Conflicts of interest

- None
Objectives

• Understand the role of the MAPK pathway in melanomagenesis
• Correlate common mutations with clinical presentation
• Review data on established and investigational inhibitors of MAPK
Metastatic Melanoma 2010

- Biopsy
  - Cutaneous
  - Uveal
  - Acral Lentiginous
  - Mucosal

- Young and Fit
  - Yes: High Dose IL2
  - No: Chemotherapy
Metastatic Melanoma 2013

Biopsy

- BRAF V600E mutant
- BRAF V600K mutant
- GNAQ or GNA11 mutant
- NRAS mutant
- Wild Type
- C-KIT mutant

Vemurafenib or Dabrafenib

Trametinib

Ipilimumab or Chemotherapy

Phase 2 data for MEK inhibition

Phase 2 data for KIT inhibition
Molecular alterations in melanoma.

Oncogenic MAPK Variants

- **c-Kit**:
  - more prevalent in mucosal melanomas and acral lentiginous melanomas.
  - Not related to UV exposure
  - <2% of melanomas.

- **RAS**:
  - *RAS* mutations in melanoma are usually *NRAS*, rather than *KRAS* or *HRAS*.
  - Tend to appear in melanomas located on sun-exposed skin and are more frequent in melanomas in older individuals.
  - 20% of melanomas.
Oncogenic MAPK Variants: BRAF

- Over 50 distinct BRAF mutations identified
- \textit{BRAFV600E}
  - substitution of valine by glutamic acid at position 600
  - over 90% of the mutations in BRAF
  - the most common point mutation in melanoma, ~ 50%
  - inversely correlated with age
- \textit{BRAFV600K}
  - the second most common BRAF mutation
  - frequency increases with age
- Other BRAF mutations can lead to decreased kinase activity…
  - but may be oncogenic through transactivation of CRAF.
Table 1. Gene mutation prevalence and molecular testing recommendations for melanoma subtypes

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Testing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First step</td>
</tr>
<tr>
<td>BRAF</td>
<td>NRAS</td>
</tr>
<tr>
<td>Cutaneous (non-CSD)</td>
<td>45%</td>
</tr>
<tr>
<td>Cutaneous (CSD)</td>
<td>5–30%</td>
</tr>
<tr>
<td>Acral</td>
<td>10–15%</td>
</tr>
<tr>
<td>Mucosal</td>
<td>5%</td>
</tr>
<tr>
<td>Uveal</td>
<td>—</td>
</tr>
<tr>
<td>Melanoma from an unknown primary</td>
<td>50%</td>
</tr>
</tbody>
</table>

NOTE: A dash (—) means "insignificant number reported"; a question mark (?) means "not yet reported."

\(^a\)Gene expression profiling and monosomy 3 analysis of primary uveal melanomas have been used as prognostic tests for metastatic risk (41); these tests currently do not have a defined role in patients with metastatic disease.
Vemurafenib
BRIM3

• Randomized, Phase 3
• Vemurafenib vs DTIC
• 675 patients
• Previously Untreated
• BRAF V600E

Vemurafenib-Response

- RECIST: 53%
- Disease control: 90%

- Vemurafenib - 5.3 months
- DTIC - 1.6 months
Vemurafenib

Median OS 13.6 months 1 year OS: 55% vs 43%
12.5 months median follow up

Dabrafenib

- RECIST: 50%
- Disease control: 92%

- Dabrafenib - 5.1 months
- DTIC - 2.7 months
BRAF Summary

Baseline

2 weeks

6 months

MEK Inhibition
Trametinib

• Open label, Randomized, Phase 3
• Trametinib vs Chemotherapy (2:1)
• 322 patients
• Previously Untreated
• BRAF V600E or V600K
• Crossover allowed
• Primary endpoint PFS, secondary endpoint OS

**MEK Inhibition**

- **Trametinib**: 4.8 months
- **DTIC**: 1.5 months

**RECIST**: 22%

**Disease control**: 78%
MEK Inhibition

Trametinib

OS at 6 months

- **Trametinib**: 81%
- **DTIC**: 67%

Hazard ratio for death, 0.54 (95% CI, 0.32–0.92)
P = 0.01
BRAF/MEK Combination

• Phase 1/2
• Dabrafenib + Trametinib
• No prior BRAFi
• BRAF V600E or V600K
• Primary endpoints: PFS, Response, and incidence of Squamous Cell Ca
• Secondary endpoint: OS, PK

BRAF/MEK Combination

• 247 patients- 85 Phase 1, 162 Phase 2
• Phase 2 1:1:1 randomization
  • Dabrafenib 150mg bid + trametinib 1 or 2mg daily, or dabrafenib monotherapy
• Crossover from monotherapy to combination therapy allowed
BRAF/MEK Combination

1 year PFS
150/2 - 41%
150 - 9%

Crossover - 80%

• Response Rate: 76% v 54%
BRAF/MEK Combination

Median OS not reached

1-year survival

150/2 - 79%
150 - 70%
Non MAPK Targeting

• Resistance to BRAF inhibition may occur through activation of a parallel pathway
  • PDGFR-β and IGF-1R
• Parallel oncogenic signaling through PI3K-Akt
• Studies combining MAPK and PI3K-Akt pathway inhibitors are in development
Key Points

• Up to 70% of melanomas have driver mutations
• The MAPK pathway is central to most melanoma
• Mutations reflect the site of disease
• Vemurafenib, dabrafenib, and trametinib are all approved for specific subtypes of melanoma
• Other targeted agents are in development
• Enrollment to clinical trials remains critical
• Thank you

• Alan Bryce

• Bryce.Alan@mayo.edu