BRAF Inhibition in Melanoma

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Disclosures

- Speaker Bureau: BMS, Genentech, Prometheus
- Advisory Board: BMS, Genentech, GSK, Eisai
Objectives

- To understand the role of BRAF mutations and the MAP kinase pathway in the pathogenesis of melanoma

- To learn the results of pivotal trials of BRAF inhibitors (vemurafenib, dabrafenib)

- To explore the use of BRAF inhibitors in patients with brain metastasis

- To learn about toxicities associated with BRAF inhibition
MAPK Pathway

Growth Factors

- RAS
- BRAF
- MEK
- ERK

Cell proliferation and survival
BRAF Mutation

Growth Factors

RAS

BRAF

MEK

ERK

Increased cell proliferation and survival

BRAF mutation is present in ~50% of melanomas
Types of BRAF Mutation

The most common mutations:

- V600E (GAG) 90%
- V600K 5-6%
- V600R 1%
- V600E2 (GAA) 0.7%
- V600D <0.1%

Arkenau HT et al. Br J Cancer. 2011 Feb 1;104(3):392-8, fig.2
Wan PT et al. 2004
MAPK and PI3K Pathway Interactions

Arkenau HT et al. Br J Cancer. 2011 Feb 1;104(3):392-8, fig.1
BRAF Inhibitors
Sorafenib

- inhibitor activities
  - CRAF - IC50 6nM
  - wt BRAF - IC50 22 nM
  - BRAFV600E - IC50 38 nM
- Phase 2 discontinuation study
- 37 patients
- 1 patient had tumor shrinkage
- Stable disease was not dependent on the presence of the BRAF mutation

Eisen T et al. Br J Cancer 2006 Sep 4;95(5):581-6, fig. 1
## The New Generation of BRAF Inhibitors

<table>
<thead>
<tr>
<th>IC50</th>
<th>vemurafenib</th>
<th>dabrafenib</th>
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</thead>
<tbody>
<tr>
<td>Wt BRAF</td>
<td>39nM</td>
<td>3.2nM</td>
</tr>
<tr>
<td>CRAF</td>
<td>16nM</td>
<td>5nM</td>
</tr>
<tr>
<td>V600E BRAF</td>
<td>8nM</td>
<td>0.65nM</td>
</tr>
<tr>
<td>V600K BRAF</td>
<td>NR</td>
<td>0.5nM</td>
</tr>
<tr>
<td>V600D BRAF</td>
<td>NR</td>
<td>1.84nM</td>
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</table>

Dabrafenib and vemurafenib Investigator's Brochure.
Vemurafenib

Phase 3 randomized trial of vemurafenib 960 mg twice a day vs dacarbazine 1000 mg/m² every 3 weeks
- 675 patients randomized 1:1
- overall survival and progression-free survival were co-primary end points

Chapman PB et al. NEJM 364;26 June 30, 2011
median progression-free survival was 5.3 months in the vemurafenib group and 1.6 months in the dacarbazine group.

Chapman PB et al. NEJM 364;26 June 30, 2011, fig. 2
At 6 months, overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group.
Updated Overall Survival

12-month survival 56% vs 44%

Chapman PB et al. ASCO 2012
Best Tumor Response (BRIM3)

**A** Vemurafenib Group

Disease Stage
- Unresectable
- M1a
- M1b
- M1c

Percent Change from Baseline in Diameters of Target Lesions

Patients Treated with Vemurafenib

RR 48%

**B** Dacarbazine Group

Disease Stage
- Unresectable
- M1a
- M1b
- M1c

Percent Change from Baseline in Diameters of Target Lesions

Patients Treated with Dacarbazine

RR 5%

Chapman PB et al. NEJM 364;26 June 30, 2011, fig. 3
Adverse Events of Vemurafenib

Adverse events led to dose modification or interruption in 129 of 336 patients (38%) in the vemurafenib group and in 44 of 282 patients (16%) in the dacarbazine group.

Chapman PB et al. NEJM 364;26 June 30, 2011, tab. 2
Dabrafenib

Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial


- Phase 3 randomized trial of dabrafenib 150 mg twice a day vs dacarbazine 1000 mg/m\(^2\) every 3 weeks
- 250 patients randomized 3:1
- The primary endpoint was progression-free survival

median progression-free survival as estimated by independent review was 6.7 months in the dabrafenib group and 2.9 months in the dacarbazine group.
Best Tumor Response
(BREAK-3)

RR 50% for dabrafenib vs 7% for dacarbazine

The estimated median duration of response was 5.5 months

Hauschild A et al, Lancet 2012 Jul 28;380(9839):358-65, fig.3
### Adverse Events of Dabrafenib


Dose reduction of dabrafenib was needed in 52 (28%) patients, and five (3%) patients discontinued drug because of adverse events.

<table>
<thead>
<tr>
<th>Any event</th>
<th>Dabrafenib</th>
<th>Dacarbazine</th>
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<tr>
<td>Any event</td>
<td>100 (53%)</td>
<td>26 (44%)</td>
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<td><strong>Skin</strong></td>
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<tr>
<td>Hyperkeratosis*</td>
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<td></td>
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<tr>
<td>Grade 2</td>
<td>23 (12%)</td>
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<td>Grade 3</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (&lt;1%)</td>
<td>0</td>
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<tr>
<td>PPE/palmar-plantar hyperkeratosis†</td>
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<tr>
<td>Grade 2</td>
<td>12 (6%)</td>
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<tr>
<td>Grade 3</td>
<td>4 (2%)</td>
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<tr>
<td>Squamous cell carcinoma/keratoacanthoma‡</td>
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<td></td>
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<tr>
<td>Grade 2</td>
<td>4 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8 (4%)</td>
<td>0</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>Nausea</td>
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<td></td>
</tr>
<tr>
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<tr>
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<tr>
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<td>3 (5%)</td>
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<tr>
<td>Grade 3</td>
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<td>Grade 2</td>
<td>0</td>
<td>2 (3%)</td>
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<tr>
<td>Grade 3</td>
<td>1 (&lt;1%)</td>
<td>3 (5%)</td>
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<tr>
<td>Grade 4</td>
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<td>4 (7%)</td>
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<td>Grade 3</td>
<td>1 (&lt;1%)</td>
<td>1 (2%)</td>
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<tr>
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<tr>
<td>Grade 3</td>
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<td>1 (2%)</td>
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<table>
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<tr>
<th>Other</th>
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<th>Dacarbazine</th>
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<tbody>
<tr>
<td>Arthralgia</td>
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</tr>
<tr>
<td>Grade 2</td>
<td>9 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (&lt;1%)</td>
<td>0</td>
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<tr>
<td>Astenia</td>
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<tr>
<td>Grade 2</td>
<td>6 (3%)</td>
<td>3 (5%)</td>
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<tr>
<td>Grade 3</td>
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<tr>
<td>Fatigue</td>
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<td>Grade 2</td>
<td>10 (5%)</td>
<td>3 (5%)</td>
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<td>Grade 3</td>
<td>2 (1%)</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Grade 2</td>
<td>9 (5%)</td>
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</tr>
<tr>
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<tr>
<td>Pyrexia</td>
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<tr>
<td>Grade 2</td>
<td>15 (8%)</td>
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<tr>
<td>Grade 3</td>
<td>5 (3%)</td>
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# Vemurafenib vs Dabrafenib – Adverse Events

<table>
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<tr>
<th>AE</th>
<th>grade</th>
<th>vemurafenib</th>
<th>dabrafenib</th>
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<td>SCC/KA</td>
<td>2</td>
<td>2%</td>
<td>2%</td>
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<tr>
<td></td>
<td>3</td>
<td>18%</td>
<td>4%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
<td>NR (&lt;5%)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3%</td>
<td></td>
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<tr>
<td>Photosensitivity</td>
<td>Any grade</td>
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<td>NR</td>
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<td>Alopecia</td>
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<td>8%</td>
<td>0%</td>
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<tr>
<td>Arthralgia</td>
<td>2</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3%</td>
<td>&lt;1%</td>
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<tr>
<td>Hyperkeratosis</td>
<td>2</td>
<td>5%</td>
<td>12%</td>
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<tr>
<td></td>
<td>3</td>
<td>1%</td>
<td>&lt;1%</td>
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<tr>
<td>Nausea</td>
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<td>7%</td>
<td>1%</td>
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<tr>
<td></td>
<td>3</td>
<td>1%</td>
<td>0%</td>
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<tr>
<td>Fatigue</td>
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<td>11%</td>
<td>5%</td>
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<td></td>
<td>3</td>
<td>2%</td>
<td>1%</td>
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<tr>
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<td>2</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Chapman PB et al. NEJM 364;26 June 30, 2011  
BRAF Inhibitors and Brain Metastasis
Dabrafenib in Patients with Brain Metastasis (BREAK-MB)

Gadolinium-enhanced T1-weighted MRI images illustrating tumor reduction

Baseline

Week 32

Kirkwood J et al. ASCO 2012
Intracranial Tumor Control (BREAK-MB)

No local treatment

Brain progression after a local treatment

Long GV et al. Lancet Oncology 2012 Nov;13(11):1087-95, fig.2, tab.2
Toxicity of BRAF Inhibitors
Cutaneous Squamous Cell Carcinoma

- Well differentiated and keratoacanthoma-like type
- Typically presented as hyperkeratotic crateriform papules on both sun-exposed and non-sun-exposed sites
- Chronically sun-damaged skin was noted in 78%
- 60% harbor RAS mutation (mainly HRAS Q61L)
- Vemurafenib – 4-31% of patients
- Dabrafenib – 6-11% of patients
- Treated by simple excision

Su F et al. NEJM 2012 Jan 19;366(3):207-15 fig.1
Paradoxical MAPK Activation

Su F et al. NEJM 2012 Jan 19;366(3):207-15 fig.3
Verrucal Keratoses

- hyperkeratotic papules similar to keratoacanthomas, warts, or smooth hyperkeratotic papules
- characterized by papillomatosis, hyperkeratosis, acanthosis, preserved granular cell layer, and low-to-moderate levels of epidermal dysplasia
- At least 49% of patients develop these lesions

Anforth R et al. Lancet Oncology 2013 Jan;14(1):e11-8 fig.2
Plantar Hyperkeratosis

- Seen in 9-10% of patients treated with vemurafenib and 8-21% treated with dabrafenib
- Distinct from hand-foot skin reaction
- Lesions only at points of pressure or friction,
- Blisters are infrequent,
- The hands are seldom involved
- Tx: urea creams, avoid friction

Anforth R et al. Lancet Oncology 2013 Jan;14(1):e11-8 fig.3
Photosensitivity

- Vemurafenib – 52%, grade 2 or 3 reactions – 12%
- Dabrafenib – not reported
- induced by ultraviolet A (UVA)
- a painful burning sensation up to 10 min after exposure
- Avoid sun (eg, wide-brim hat, long sleeves, broad spectrum sunscreen that covers UVA spectrum)
- the reaction can be triggered behind windows

Anforth R et al. Lancet Oncology 2013
Other Skin Toxicities

- Grover's disease (a benign acantholytic disorder that presents as several scattered erythematosus papules, some eroded, with variable degrees of itch) – 27%
- alopecia (8–36%),
- changes in the structure of the hair (17%),
- folliculitis (9%),
- keratosis pilaris
- panniculitis

Anforth R et al. Lancet Oncology 2013 Jan;14(1):e11-8 fig.3
Pyrexia

- Dabrafenib – 11-30%
- Vemurafenib – 18%
- Dabrafenib + trametinib – 70%

- Fever was not associated with age, sex, BRAF genotype, M-stage, sites of distant metastases, baseline LDH and baseline tumor volume
- Fever did not predict response, PFS or OS.
- Accompanied by a transient elevation of AST, ALT, alkaline phosphatase, LDH

TX:
- Dose reduction - not effective
- anti-pyretics (acetaminophen, NSAIDs) - not effective
- corticosteroids – most effective

Lee CI et al. ASCO 2012
New primary melanomas were reported in a cohort of five patients given vemurafenib. All melanomas were wild-type BRAF lesions.

12 newly detected primary cutaneous melanomas in patients given vemurafenib or dabrafenib. All were wild-type BRAF.

Dalle S et al. NEJM 2011
Zimmer L et al. JCO 2012
Noncutaneous BRAF Inhibitor-induced Neoplasia

- Colonic adenomas, gastric polyps
  Four of 8 patients treated for more than 2 years underwent esophagogastroduodenoscopy and colonoscopy
  Three patients had multiple colonic adenomas and/or hyperplastic gastric polyps

- NRAS-mutated chronic myelomonocytic leukemia
  A patient with metastatic melanoma developed leukocytosis of 80,000 11 days after starting vemurafenib

Chapman P et al. SMR 2012
Callahan MK et al. NEJM 2012 Dec 13;367(24):2316-21 fig.1
Other RAF Inhibitors

- **RAF265**
  - Phase 1 study completed (ASCO 2011)
  - Phase 1 of RAF265+MEK162 in BRAF/NRAS mutated tumors

- **LGX818**
  - Phase 1 study in BRAF mutated melanoma
  - Phase 1b/2 of LGX818+MEK162 in BRAF mutated tumors

- **XL281/BMS908662**
  - Phase 1 study completed (ASCO 2009)

- **ARQ736**
  - Phase 1 study in BRAF/NRAS mutated tumors

- **GDC0879** - preclinical
- **AZ628** - preclinical
- **PF04880594** - preclinical
Summary

- 50-60% of metastatic melanomas harbor V600 BRAF mutation that leads to constitutive activation of MAPK pathway

- Vemurafenib and dabrafenib are effective BRAF inhibitors with a response rate of approximately 50% (by RECIST), but eventually tumors develop resistance to the therapy

- The treatment is associated with unique side effects and dose reduction or interruption is often required