BRAF pathway

Sun Young Kim
Division of Medical Oncology
Center for Colorectal Cancer
National Cancer Center
Contents

- BRAF inhibitor in advanced melanoma
- Paradoxical MAPK pathway activation by BRAF inhibitor
- BRAF inhibitor resistance
- Intrinsic resistance to BRAF inhibitor in colorectal cancer
- Thyroid /NSCLC/hairy cell leukemia
## Frequency of BRAF Mutations in Various Cancers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>% of pts with BRAF Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>30-70</td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>40-70</td>
</tr>
<tr>
<td>Cisplatin-refractory testicular cancer</td>
<td>25</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>10-20</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5-20</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>5-10</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>5-10</td>
</tr>
<tr>
<td>Glioblastoma, NSCLC, HNSCC, breast cancer, pancreatic cancer</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Relative frequency of BRAF mutations according to location

Most oncogenic mutations occur in exon 11 and 15, which are in the kinase domain.

<table>
<thead>
<tr>
<th>Mutation location</th>
<th>% of all BRAF mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>V600E</td>
<td>97.3%</td>
</tr>
<tr>
<td>V600K</td>
<td>1.0%</td>
</tr>
<tr>
<td>K601E</td>
<td>0.4%</td>
</tr>
<tr>
<td>G469A</td>
<td>0.4%</td>
</tr>
<tr>
<td>D594G</td>
<td>0.3%</td>
</tr>
<tr>
<td>V600R</td>
<td>0.3%</td>
</tr>
<tr>
<td>L597V</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

V, valine; E, glutamic acid; K, lysine; G, glycine; A, alanine; D, aspartic acid; G, glycine; R, arginine; L, leucine.

Blockade of MAPK pathway

Type I BRAF inhibitors
- selective B-Raf inhibitors:
  - PLX4032
  - GSK2118436
- selective MEK inhibitors:
  - PD0325901
  - AZD6244
  - GSK1120212

Type II BRAF inhibitors
- non-selective Raf inhibitors:
  - sorafenib
  - RAF-265
  - XL281

### Sorafenib: ineffective in melanoma

<table>
<thead>
<tr>
<th></th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>Randomized discontinuation trial: SD at 12w randomized into sorafenib vs placebo</td>
<td>Carboplatin + paclitaxel (CP) vs carboplatin + paclitaxel + sorafenib (CPS)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>37</td>
<td>823</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Among 34 evaluable pts, 1 PR 6 SD 27 PD</td>
<td>OS (1° endpoint): 11.3 mo (CP) v 11.1 mo (CPS)</td>
</tr>
</tbody>
</table>


Vemurafenib (PLX-4032, Zelboraf)

**IC$_{50}$ nM**

<table>
<thead>
<tr>
<th>Description</th>
<th>IC$_{50}$ nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-RAF (V600E)</td>
<td>31</td>
</tr>
<tr>
<td>C-RAF</td>
<td>48</td>
</tr>
<tr>
<td>B-RAF WT</td>
<td>100</td>
</tr>
</tbody>
</table>

**Effect of PLX4032 on COLO205 xenograft**

Phase I study of vemurafenib

- Dose-escalating cohort (N=55)
  - 49 melanoma, 3 PTC, 3 others
- Dose-limiting toxicities
  - Arthralgia, fatigue, rash
- RP2D = 960mg bid
- Extension cohort (N=32)
  - All BRAF V600E melanoma

<table>
<thead>
<tr>
<th></th>
<th>N=87</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>14 (16%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (12%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (3%)</td>
<td>5 (5%)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (5%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>6 (7%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (9%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>cuSCC</td>
<td>0%</td>
<td>18 (21%)</td>
<td></td>
</tr>
<tr>
<td>Palma-plantar dysesthesia</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

Tumor response in extension cohort of phase I trial of vemurafenib

Pharmacodynamic study of vemurafenib

In patients with tumour regressions, pathway analysis typically showed greater than 80% inhibition of cytoplasmic ERK phosphorylation.

Vemurafenib phase III trial: BRIM-3

Prev untreated
Stage III/IV BRAF(V600) melanoma
Co-primary endpoint: OS and PFS

Vemurafenib (960mg bid daily)
N=337

Dacarbazine (1000mg/m² q 3 weeks)
N=338

Median PFS: 5.3m v 1.6m (2011) → 6.9 m v 1.6m (2014)

Vemurafenib phase III trial: BRIM-3

**ORR**
48% (vemurafenib) vs 5% (dacarbazine)

Vemurafenib phase III trial: BRIM-3

6-mo OS: 84% vs 64% (2011)

OS 13.6m v 9.7m (2014) after median F/U of 12.5 mo

Open-label safety study of vemurafenib (n=3,222)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grades 1 and 2</th>
<th>Grades 3 and 4</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one adverse</td>
<td>2981 (93%)</td>
<td>1480 (46%)</td>
<td>3052 (95%)</td>
</tr>
<tr>
<td>event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>1537 (48%)</td>
<td>155 (5%)</td>
<td>1592 (49%)</td>
</tr>
<tr>
<td>Arthralgia†</td>
<td>1222 (38%)</td>
<td>106 (3%)</td>
<td>1259 (39%)</td>
</tr>
<tr>
<td>Fatigue‡</td>
<td>1042 (32%)</td>
<td>93 (3%)</td>
<td>1093 (34%)</td>
</tr>
<tr>
<td>Photosensitivity reaction§</td>
<td>959 (30%)</td>
<td>69 (2%)</td>
<td>994 (31%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>823 (26%)</td>
<td>4 (&lt;1%)</td>
<td>826 (26%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>610 (19%)</td>
<td>34 (1%)</td>
<td>628 (19%)</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>621 (19%)</td>
<td>7 (&lt;1%)</td>
<td>624 (19%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>483 (15%)</td>
<td>31 (&lt;1%)</td>
<td>499 (16%)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>477 (15%)</td>
<td>8 (&lt;1%)</td>
<td>484 (15%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>454 (14%)</td>
<td>0</td>
<td>455 (14%)</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma¶</td>
<td>75 (2%)</td>
<td>389 (12%)</td>
<td>437 (14%)</td>
</tr>
</tbody>
</table>
Skin toxicities of RAF inhibitors

CuSCC

Verrucal keratoses

Figure 3: Plantar hyperkeratosis, Grover’s disease, and hair-follicle changes
(A) Plantar hyperkeratosis; (B) Grover’s disease; (C) curly and grey hair; (D) and keratosi pilaris-like eruption.

## Cutaneous toxicity of RAF inhibitors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence associated with drug</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>Sorafenib</td>
<td>Vermrafenib</td>
</tr>
<tr>
<td>cuSCC</td>
<td>6-7%</td>
<td>18-31%</td>
</tr>
<tr>
<td>Verrucal keratosis</td>
<td>NR</td>
<td>Present*</td>
</tr>
<tr>
<td>Grover’s disease</td>
<td>NR</td>
<td>Present†</td>
</tr>
<tr>
<td>Folliculocenttric exantema; keratosis pilaris-like reaction</td>
<td>Present</td>
<td>Present†</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>NR</td>
<td>Present</td>
</tr>
<tr>
<td>Hair changes</td>
<td>27%</td>
<td>8-36%</td>
</tr>
<tr>
<td>Panniculitis</td>
<td>NR</td>
<td>Present</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>NR</td>
<td>52%</td>
</tr>
<tr>
<td>Plantar hyperkeratosis</td>
<td>Present</td>
<td>9-10%</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>77%</td>
<td>NR</td>
</tr>
</tbody>
</table>

cuSCC=cutaneous squamous-cell carcinoma. Present=event has been reported but frequency is unknown. NR=not reported. UVA=Ultraviolet A. *Skin papilloma reported in 29% of patients in phase 2 trial. †Rash reported in 3-52% of patients in vemurafenib phase 1, 2, and 3 trials.

**Table 2:** Cutaneous events associated with RAF inhibiting agents and their management

Dabrafenib (Tafinlar): phase I trial (BREAK-I)

- N=184 (including 156 melanoma)
- MTD was not reached up to 300mg bid: d/t dose-limiting effects were seen in minority of pts taking 200mg bid and 300mg bid, 150mg bid was selected as RP2D

<table>
<thead>
<tr>
<th></th>
<th>IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF$^{V600E}$</td>
<td>0.65</td>
</tr>
<tr>
<td>BRAF$^{WT}$</td>
<td>3.2</td>
</tr>
<tr>
<td>CRAF</td>
<td>5.0</td>
</tr>
</tbody>
</table>

36 treated with RP2D → PR or CR in 26(69%)

**Dabrafenib: phase III trial (BREAK-3)**

Stage III/IV BRAF\textsuperscript{V600E} melanoma

Primary endpoint: PFS

- Dabrafenib (150mg bid)  
  N=187

- Dacarbazine (1000mg/m\textsuperscript{2} q 3 weeks)  
  N=63

PFS 5.1m v 2.7m in 2012 (HR 0.30, 95% CI 0.18 – 0.51)  
\( \Rightarrow \) 6.9m v 2.7m in 2013 (HR 0.37, 95% 0.23-0.57)

ORR: 50% v 6%

Hauschild et al, ASCO #9013
OS from BREAK-3, a phase III trial of dabrafenib

Improved survival in dacarbazine arm d/t
- cross-over to dabrafenib (59%)
- treatment with vemurafenib (10%).

OS 18.2m v 15.6m
(HR 0.76, 95% CI 0.48 – 1.21)

Hauschild et al, ASCO 2013 #9013
## Dabrafenib vs. Vemurafenib: safety profile

<table>
<thead>
<tr>
<th>toxicity</th>
<th>Grade</th>
<th>Dabrafenib (BREAK-3)</th>
<th>Vemurafenib (BRIM-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuSCC</td>
<td>Grade 2</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>Grade 2</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>fatigue</td>
<td>Grade 2</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>arthralgia</td>
<td>Grade 2</td>
<td>5%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>nausea</td>
<td>Grade 2</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>pyrexia</td>
<td>Grade 2</td>
<td>8%</td>
<td>10%*</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>3%</td>
<td>&lt;1%†</td>
</tr>
</tbody>
</table>

*Grade 1-2 from open-label safety study  
†Grade 3-4 from open-label safety study
BRAFi for brain mets from melanoma

- 9/10 pts with asymptomatic brain mets showed tumor regression in phase I trial of dabrafenib
- In a phase II trial for pts with brain mets (BREAK-BM), intracranial response was noted irrespective whether they are untreated or have been prev treated but have progressed.
- Vemurafenib also showed incracranial response (40%) for symptomatic brain mets

Prev Untreated: CR+ PR in 39.2% (29/74)

Prev local treatment: CR + PR in 30.8% (20/65)

RAF inhibitors activate MAPK pathway in RAS\textsuperscript{mt} or RAF\textsuperscript{wt}

Paradoxical activation of MAPK pathway

Dimerization of RAF isotypes \(\rightarrow\) activation of MEK via CRAF in RAS-dependent manner

MAPK activation d/t BRAF inhibitor binding?

Inhibitor binding activates wild-type RAF isoforms by inducing dimerization, membrane localization and interaction with RAS-GTP through conformational effects on RAF kinase domain.


MAPK activation d/t kinase-dead BRAF?

In the presence of oncogenic RAS, BRAF is cytosolic in an inactive conformation & CRAF is recruited to the plasma membrane by RAS and activates the pathway.

BRAF is no longer autoinhibited and is recruited to the plasma membrane by RAS and binds to CRAF. Although BRAF does not itself signal, it can act as a scaffold to enhance CRAF activity and consequently enhance signaling through the pathway.

RAS gene mutations (HRAS, NRAS or KRAS) in 21 specimens out of 35 cuSCC samples (60%) from BRAFi-treated patients: 12 specimens had HRAS codon 61 mutation

cuSCC generation with BRAFi in HRAS mutated lesion in mouse model

- Two-stage skin carcinogenesis mouse model
  - Carcinogen (DMBA): induce HRAS Q61L mutation in mouse keratinocytes
  - Tumor promotor (TPA): induce cuSCC
- Treatment with BRAFi (PLX4720) with DMBA + TPA: markedly accelerated tumor growth
- Addition of PD184352 (MEKi) suppressed tumor development in mice given DMBA, TPA and PLX4720

Secondary malignancy during BRAFi treatment

- **chronic myelomonocytic leukemia**
  - Reported in a vemurafenib-treated melanoma pt
  - Habouring NRAS-mutation (G12R)
  - Vemurafenib might have stimulate the growth of preexisting (clinically undiagnosed) NRAS-mutated CMML cells

- **New primary melanoma (NPM)**
  - Incidence: vemurafenib 2.4%, dabrafenib 1.6% in phase III trials
  - Higher compared to incidence of NPM in pre-BRAFi era (0.4% at 1-year in stage IV melanoma)

BRAF + MEK dual blockade

- Trametinib: a potent, highly specific inhibitor of MEK1/MEK2
- Dabrafenib + Trametinib was granted accelerated approval for BRAF V600E/V600K melanoma pts based on the results of Phase I/II trial on Feb 2014

Dabrafenib 150mg bid
N=54
Dabrafenib 150mg bid + trametinib 1mg qd
N=54
Dabrafenib 150mg bid + trametinib 2mg qd
N=54

## Toxicity profile: Dabrafenib vs CombiDT

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grade 3 or 4</th>
<th>Any grade</th>
<th>Dabrafenib (n=53)</th>
<th>CombiDT 150/1 (n=54)</th>
<th>CombiDT 150/2 (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>26%</td>
<td>0</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>69%</td>
<td>71%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Grade 3 or 4</td>
<td>0</td>
<td>4%</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ EF</td>
<td>Grade 3 or 4</td>
<td>0</td>
<td>0</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td></td>
<td></td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Chorioretinopathy</td>
<td>Any grade</td>
<td>0</td>
<td>0</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Grade 3 or 4</td>
<td>0</td>
<td>15%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td></td>
<td></td>
<td>43%</td>
<td>40%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Any grade</td>
<td>34%</td>
<td>44%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Any grade</td>
<td>36%</td>
<td>20%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>Any grade</td>
<td>30%</td>
<td>6%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Any grade</td>
<td>34%</td>
<td>9%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>cuSCC</td>
<td>Grade 3 or 4</td>
<td>17%</td>
<td>2%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td>19%</td>
<td>2%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

MAPK inhibitors for BRAF-mutated melanoma

Resistance mechanism of BRAFi and MEKi might be similar: one drug after progression on the other is unlikely to reslut in tumor regression.
Mechanism of resistance to BRAF inhibitors

No secondary mutation in BRAFV600E
MAPK reactivation driven by secondary mutations in NRAS
Pharmacodynamic analysis of tissues from BRIM-2 participants

Spectrum of BRAF inhibitor resistance mechanism
Analysis of 59 biopsies from progressing lesions after vemurafenib or dabrafenib

BRAF V600E mutation in CRC

- 5-20% of CRC
- Mutually exclusive with KRAS mutation
- Poor prognostic marker
- Associated with female, proximal colon, MSI-H, and hyper-methylation

Roth et al, JCO 2010
BRAF mutation in CRC: predictive of EGFRi efficacy?

Pretreated pts (n=79 KRAS WT including 11 BRAF mutants)

Untreated pts (1st line setting) (n=625 KRAS WT including 59 BRAF mutants)

BRAF inhibitor for BRAF-mutated CRC
extension cohort from a phase I trial of PLX4032

Metastatic CRC
BRAF+ V600E+

N=21

PLX4032
(vemurafenib)

Endpoints
1\textsuperscript{st}: ORR (overall response rate)
2\textsuperscript{nd}: PFS, Safety, PK, PD

- 1 PR + 8 SD (including 4 mixed responses): RR 5%
- PFS 3.7m
- The activity appears to be minimal, in contrast to the activity reported in BRAF-mutated melanoma

Kopetz et al, ASCO 2010 # 3534
CRC vs melanoma
decreased sensitivity to vemurafenib in CRC

Rapid ERK reactivation after treating vemurafenib in CRC: via RTK activation

Corcoran et al, Cancer Discovery 2012
Negative feedback btw pERK and EGFR in CRC

Phosphatase activity

“EGFR-expressing colorectal cancer cells are thus ‘primed’ for resistance to BRAF inhibitors. “

EGFR + BRAF blockade: synergize to induce apoptosis and to suppress CRC tumor growth

Dabrafenib + Trametinib for BRAF mutated CRC: phase I/II trial

- 5 PR (12%), 22 SD (51%) including 11 minor responses (26%)
- 10 (23%) remained on study >6 mo
- MAPK signaling inhibited but lesser degree than observed in BRAF mutated melanoma

Figure 2. Waterfall Plot of Investigator-Assessed Maximum Reduction from Baseline Tumor Measurement (N = 43)

Note: horizontal reference lines are at −30% and 20%
Dabrafenib + Trametinib + Panitumumab for BRAF mutated CRC: phase I/II trial

D+T+P: Well tolerated at the full, approved monotherapy doses for all 3 agents (150/2 + Pmab 6mg/kg biweekly)- no DLT have not occurred

<table>
<thead>
<tr>
<th>Tx-treated Aes for D+T+P (N=16)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acneiform rash</td>
<td>4 (25%)</td>
<td>4 (25%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (44%)</td>
<td>0</td>
<td>1(6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (31%)</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (25%)</td>
<td>2 (13%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>3 (19%)</td>
<td>2 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin fissures</td>
<td>3 (19%)</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>pyrexia</td>
<td>2 (13%)</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>
D+P+T may provide more robust inhibition of ERK in BRAF mutated CRC

Figure 6. Cross-Study Comparison of Phospho-ERK Modulation Between D+P, D+T and D+P+T Therapy in CRC and D Therapy in Melanoma

Comparison of pERK modulation using D-based combination therapies in BRAFm CRC and BRAFm melanoma. Treatment in BRAFm CRC was D (150 mg BID), T (1.5-2 mg QD) and/or P (4.5-6 mg Q2W). Treatment in BRAFm melanoma was D (70-200 mg BID). Average ± SD for median pERK decrease in CRC was D+P (n = 8): -12% (± 33.2%), -23%; D+T (n = 9): 47% (± 24%), -36.7%; D+P+T (n = 4): -69% (± 19.3%), -64.5%. Average ± SD for pERK decrease in melanoma was D (n = 8): 76% (± 20%), -84%.
Thyroid cancer

- BRAF mutation
  - 30-70% of PTC
  - 20-25% in anaplastic thyroid cancer
- BRAF mutation is known to be associated with poor clinicopathological outcomes (extrathyroidal invasion, lymph node metastasis, advanced stage at initial surgery) and independently predict recurrence
Sorafenib for differentiated thyroid cancer: DECISION trial

radioiodine-refractory, metastatic differentiated thyroid cancer

Primary endpoint: PFS

Neither BRAF nor RAS mutation status was predictive of sorafenib benefit for progression-free survival

<table>
<thead>
<tr>
<th>genotype</th>
<th>Group</th>
<th>mPFS</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF-mutated</td>
<td>Sorafenib (n=34)</td>
<td>20.5m</td>
<td>0.46 (0.24-0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=43)</td>
<td>9.4m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF-wild type</td>
<td>Sorafenib (n=92)</td>
<td>8.9m</td>
<td>0.55 (0.38-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=87)</td>
<td>3.8m</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

interaction btw BRAF and PFS: p = 0.653

Vemurafenib for BRAF-mutated PTC

- A Phase II trial (NCT01286753, NO25530)
  - Enrolled 51 BRAF\textsuperscript{V600E} mutated PTC pts
  - Primary endpoint: best overall response in C1

<table>
<thead>
<tr>
<th></th>
<th>C1 (TKI-naïve) N=26</th>
<th>C2 (TKI-treated) N=25*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td>35%</td>
<td>26%</td>
</tr>
<tr>
<td>mPFS</td>
<td>15.6m</td>
<td>6.8m</td>
</tr>
</tbody>
</table>

*21 pts were sorafenib-treated

Brose et al, European Cancer Congress 2013, Abstr #28
Anaplastic thyroid cancer

A case report

51-year-male, anaplastic thyroid cancer with BRAF V600E mutation
s/p thyroidectomy and tracheostomy, s/p paclitaxel + carboplatin
Progressive dyspnea, hypoxia → vemurafenib was started

Lung adenocarcinoma harboring BRAF mutations

- BRAF mutation detected in 18 (3%) out of 697 MSKCC case series
- All 18 pts were current or former smokers
- All 18 pts were white (relatively uncommon in nonwhite population; 1.3% in Japanese)
- None had concomitant mutations in EGFR or KRAS or a translocation in ALK
- Relatively smaller portion of V600E

Phase II trial of Dabrafenib in $\text{BRAF}^{\text{V600E}}$ NSCLC: BRF113928

Primary objective: investigator-assessed ORR

- **NSCLC**
  - BRAF V600E mutation
  - $\geq 1$ line prior tx

- **Stage 1**
  - N=20

- **Stage 2**
  - N=20

- Dabrafenib 150mg twice daily

**Interim analysis:**
- Response in 8 PR out of 20 stage 1 pts (RR=40%)

Planchard et al, ASCO 2013 #8009
Hairy cell leukemia

All 48 HCL pts showed BRAF V600E mutation

Take home message

- **BRAF-mutated Melanoma**
  - Vemurafenib / Dabrafenib: RR 40-50%, PFS 5-7m
  - Class toxicities: Arthralgia, rash, hyperkeratosis, alopecia
  - cutaneous SqCC by paradoxical MAPK pathway activation
  - Dual BRAF+ MEK blockade with Dabrafenib + Trametinib
    - RR 76%, PFS 9.4m, ↓cuSCC
  - Resistance mechanism: MAPK-dependent vs MAPK-independent

- **BRAF-mutated Colorectal Cancer**
  - BRAFi monotherapy is NOT effective d/t activation of EGFR
  - Strategy of adding MEKi and/or anti-EGFR Ab might be promising

- **BRAF-mutated thyroid cancer**
  - Benefit of sorafenib is not restricted to BRAF-mutated DTC
Quiz 1

다음 중 BRAF mutation의 빈도와 암종이 잘못 짝지어진 것은?

1) Melanoma 30-70%
2) Colorectal cancer 5-20%
3) Nonsmall cell lung cancer 1-5%
4) Papillary thyroid cancer 40-70%
5) Breast cancer 10-20%
Quiz 2

BRAF-mutated metastatic melanoma에서 사용되는 약제에 대해 맞는 설명으로 짝지어진 것은?

가 Vemurafenib은 type I BRAF inhibitor로서 단독치료시 6.9개월의 무진행 생존기간을 보여 dacarbazine 치료에서의 1.6개월에 비해 유의한 연장을 보였다.

나 BRAF inhibitor 투여 후 진행한 경우, MEK inhibitor를 이용한 이차요법으로 생존기간의 연장을 기대할 수 있다.

다 Dabrafenib + trametinib 병용치료시 피부의 편평상피세포암의 빈도가 dabrafenib 단독치료에 비해 감소하였다.

라 Dabrafenib 투여중 발생하는 피부의 편평상피세포암은 원격전이가 흔하고 예후가 나쁘며, 이 경우 dabrafenib을 중단해야 한다.

1) 가, 나, 다 2) 가, 다 3) 나, 라 4) 라 5) 가,나,다,라
Quiz 3

다음 중 BRAF inhibitor에 대한 내성기전으로 알려져 있지 않은 것은?

1) RAS mutation
2) COT kinase overexpression
3) MEK1 mutation
4) Secondary BRAF mutation
5) PDGFRB upregulation
다음 중 설명으로 맞지 않는 것은?

가. BRAF inhibitor로 인한 MAPK pathway의 paradoxical activation은 치료 중 피부의 편평상피세포암 발생의 기전이 된다.
나. Vemurafenib은 dabrafenib에 비해 발열반응이 더 흔하게 나타난다.
다. BRAF inhibitor 치료 중 발생한 피부 편평상피세포암에서는 RAS mutation이 흔히 발견된다.
라. Dabrafenib은 분자량이 커서 blood-brain barrier를 통과하지 않으므로 melanoma에서 발생한 brain metastasis에는 효과가 없다.

1) 가, 나, 다  2) 가, 다  3) 나, 라  4) 라  5) 가, 나, 다, 라
대장암에서의 BRAF mutation 및 약제 사용에 대한 설명이다. 맞는 것으로 짝지어진 것은?

가. BRAF mutation이 있는 대장암에서 vemurafenib 치료는 반응률 5% 정도로서, 동일한 유전자변이가 있는 흑색종에서의 치료성적에 비해 좋지 않다.
나. 전이성 대장암에서 BRAF mutation의 존재는 짧은 생존기간을 예측하는 나쁜 예후인자이다.
다. 같은 BRAF mutation이 있는 종양이어도 대장암에서 BRAF 억제제 단독으로 치료효과를 얻기 어려운 이유는 EGFR 발현이 흑색종에 비해 높은 것과 연관이 있다.
라. 대장암에서 BRAF mutation은 종양의 위치가 하행결장 및 직장일 때 흔히 발견된다.

1) 가, 나, 다  2) 가, 다  3) 나, 라  4) 라  5) 가, 나, 다, 라