BRAF IN NSCLC

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Disclosures

I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack, Merck Serono, MSD, Amgen, Clovis, Astellas and Tesaro, for which I received honoraria.

I declare no conflict of interest.
NSCLC Drivers

- SCLC
- Other squamous
- PDGFRA
- FGFRs
- DDR2
- EGFR vIII
- Large
- Other adeno.
- EGFR
- KRAS
- ALK
- HER2
- BRAF
- MEK1
- MET
- RET
- ROS1

Courtesy Suda and Mitsudomi 2013
Definition of drivers?

Mouse models for \textit{BRAF}-induced cancers

C. Pritchard\textsuperscript{1}, L. Carragher, V. Aldridge, S. Giblett, H. Jin, C. Foster, C. Andreadi and T. Kamata

Department of Biochemistry, Henry Wellcome Building, University of Leicester, Lancaster Road, Leicester LE1 7RH, U.K.

Cre-mediated activation in lung indicate that (V600E)\textit{BRAF} mutation can drive tumour initiation and that its primary effect is to induce high levels of cyclin D1-mediated cell proliferation
Oncogenic vs canonical signalling

Growth, cell cycle upregulation, anti-apoptosis, angiogenesis, metabolic regulation, immune suppression

Sullivan, Eur J Cancer 2012
First evidences of BRAF V600E mutations
• BRAF missense mutations in exons 11 or 15 are evidenced in 2-5% of NSCLC
• > 50% of NSCLC BRAF mutations are non-V600E (G469A (40%), D594G (10%))
• V600E mutations might be correlated to non-smoking habit while the contrary might hold true for exon 11 mutations
BRAF-related prognosis in resected NSCLC

BRAF mutations in 36 ADCs (4.9%) and one SCC (0.3%). 56.8% were V600E, and 43.2% were non-V600E.

V600E mutations were significantly more prevalent in females and an aggressive micropapillary subtype with shorter disease-free and overall survival rate.

Marchetti JCO 2011
BRAF Mutated Lung Cancer: Clinical Features and Outcomes

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>697</td>
<td>1046</td>
<td>883</td>
<td>951</td>
<td>NA</td>
<td>979</td>
</tr>
<tr>
<td>BRAF n (%)</td>
<td>18 (3)</td>
<td>36 (3.5)</td>
<td>36 (4)</td>
<td>21 (2)</td>
<td>63 (NA)</td>
<td>17 (1.7) (AC 2.3)</td>
</tr>
<tr>
<td>V600E</td>
<td>50%</td>
<td>58%</td>
<td>50%</td>
<td>81%</td>
<td>57%</td>
<td>V600E only</td>
</tr>
<tr>
<td>Smoking</td>
<td>smokers</td>
<td>never smokers</td>
<td>no difference</td>
<td>smokers</td>
<td>smokers</td>
<td>71% (ex-) smokers</td>
</tr>
<tr>
<td>Survival</td>
<td>same</td>
<td>worse</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>NA</td>
</tr>
<tr>
<td>Comparator</td>
<td>EGFR/ALK / KRAS+</td>
<td>BRAF WT</td>
<td>BRAF/EGFR/ KRAS/ALK WT</td>
<td>other drivers</td>
<td>EGFR/KR AS+</td>
<td>NA</td>
</tr>
</tbody>
</table>

Clinical Characteristics and Course of 63 Patients with 
*BRAF* Mutant Lung Cancers

Anya M. Litvak, MD,* Paul K. Paik, MD,* Kaitlin M. Woo, MS,† Camelia S. Sima, MD,† Matthew D. Hellmann, MD,* Maria E. Arcila, MD,‡ Marc Ladanyi, MD, PhD,‡ Charles M. Rudin, MD, PhD,* Mark G. Kris, MD,* and Gregory J. Riely, MD, PhD*

- **V600** had a better survival than non-V600 (3-year OS: 24% versus 0%; \( p < 0.001 \)).

**Clinical Cancer Research**

Clinical, Pathologic, and Biologic Features Associated with *BRAF* Mutations in Non–Small Cell Lung Cancer

Stephanie Cardarella, Atsuko Ogino, Mizuki Nishino, et al.

- Within the BRAF cohort, patients with **V600E-mutated tumors** had a shorter PFS to platinum-based chemotherapy compared with those with non-V600E mutations (4.1 vs. 8.9 months; NS)
BRAF mutation type according to tumour stage?

Stage I-III A
- V600E: 41%
- G469A: 34%
- G469V: 19%
- V600M: 3%
- D594G: 3%

Stage III B/IV
- V600E: 71%
- G469A: 13%
- D594G: 10%
- G469V: 6%

Litvak, J Thor Oncol 2014
Sorafenib stabilises the enzyme in inactive conformation of the kinase (Type 2-binding model), whereas the other inhibitors stabilise the enzyme with the DFG-loop in the ATP pocket (Type 1-binding model).

All of these inhibitors are less-potent inhibitors of RAF–MEK–ERK signalling in cells expressing wild-type BRAF and in fact paradoxically activate the pathway, especially in cells with activating RAS mutations.
**BRAF V600E type I inhibitors: Vemurafenib**

- Vemurafenib is a first in class inhibitor targeting activated BRAF V600E kinase (type I inhibitor)
- Kinome specificity profile:
  
  ![Kinome specificity profile diagram](image)

  **Table:**

<table>
<thead>
<tr>
<th>Target Kinase</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E</td>
<td>31</td>
</tr>
<tr>
<td>BRAF WT</td>
<td>100</td>
</tr>
<tr>
<td>CRAF</td>
<td>48</td>
</tr>
</tbody>
</table>


  Bollag & al. *Nature* 2010

- FDA and EMA approved: 2011/12
Dramatic Response Induced by Vemurafenib in a *BRAF* V600E-Mutated Lung Adenocarcinoma
A Patient With BRAF V600E Lung Adenocarcinoma Responding to Vemurafenib

Oliver Gautschi, MD, * Chantal Pauli, MD, † Klaus Strobel, MD, ‡ Astrid Hirschmann, † Gert Printzen, MD, § Stefan Aebi, MD, * and Joachim Diebold, MD †

Case report

BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib

Sara D. Robinson a, Joyce A. O'Shaughnessy a,b, C. Lance Cowey a,b, Kartik Konduri a,b,*

Lung adenocarcinoma with BRAF G469L mutation refractory to vemurafenib

Oliver Gautschi a,* Solange Peters e, Vincent Zoete e, Franziska Aebersold-Keller b, Klaus Strobel c, Bernhard Schwizer d, Astrid Hirschmann b, Olivier Michielin e, Joachim Diebold b
VE-BASKET: A First-in-Kind, Phase 2, Histology-Independent “BASKET” Study of Vemurafenib in Non-melanoma Solid Tumors Harboring \(BRAF^{V600}\) Mutations

- Simon 2-stage adaptive design\(^1\)
  - 7 Cohorts (metastatic solid tumors and multiple myeloma)
  - Up to 170 pts
  - \(BRAF^{V600}\) positive (testing per local methods)
  - Vemurafenib 960 mg BID orally
  - Primary Endpoint: RR at Week 8
  - Secondary Endpoints: PFS, TTP, BOR, TTR, DOR, CBR, OS, safety

Primary endpoint: response rate at Week 8
Secondary endpoints: PFS, TTP, BOR, TTR, DOR, CBR, OS, safety

ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; NSCLC, non-small cell lung cancer.

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2. Tabernero J et al. ASCO Meeting abstract #3518 to be presented Saturday, May 31, 2014.
Presented by: David M. Hyman

ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; NSCLC, non-small cell lung carcinoma; PD-NSC carc., poorly differentiated non-small cell carcinoma.

*Only includes patients who had measurable disease at baseline based on RECIST and at least 1 posttreatment evaluation.*
# Preliminary Efficacy Evaluation: Best Overall Response

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NSCLC (n=19)</th>
<th>CLC (n=7)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ECD/LCH (n=11)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of Analysis</strong></td>
<td><strong>Best Confirmed Overall Response</strong></td>
<td>Unconfirmed Preliminary Overall Response at Week 8</td>
<td><strong>Best Confirmed Overall Response</strong></td>
</tr>
<tr>
<td>Complete response</td>
<td>–</td>
<td>–</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (42.1)</td>
<td>–</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 (31.6)</td>
<td>4 (57.1)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (15.8)</td>
<td>3 (42.9)</td>
<td>–</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (10.5)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
<td>1 (9.1)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Clinical benefit</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>14 (73.7)</td>
<td>4 (57.1)</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>48.8-90.9</td>
<td>18.4-90.1</td>
<td>58.7-99.8</td>
</tr>
</tbody>
</table>

CI, confidence interval; CLC, cholangiocarcinoma; CR, complete response; ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; NSCLC, non-small cell lung carcinoma; PR, partial response; SD, stable disease.

<sup>a</sup>Unconfirmed preliminary overall response at Week 8. In cohort 4 (CLC), 2 patients had a late response (PR) at Week 24 (unconfirmed) and Week 16 (confirmed).

<sup>b</sup>Table includes only patients who had measurable disease at baseline and at least 1 posttreatment evaluation based on RECIST.

<sup>c</sup>1 patient died and 1 patient withdrew consent before Week 8 evaluation.

<sup>d</sup>Patient withdrew from study because of an adverse event before Week 8 evaluation.

<sup>e</sup>Clinical benefit = PR, CR, or SD.

Presented by: David M. Hyman
Time to Response and Progression

![Graph showing time to response and progression with time on the x-axis and patients treated with study drug on the y-axis. The graph illustrates the time to progression (PR), stable disease (SD), and progression disease (PD) for each patient. Symbols representing time to response (PR), time to progression (PD), and alive (AL) are used to track progression and outcomes.]
BRAF V600E type I inhibitors: Dabrafenib

Mode of Action
• Reversible, small molecule
• ATP competitive

Molecular Activity:
BRAF V600E: IC$_{50}$ 0.65 nM
BRAF WT: IC$_{50}$ 3.2 nM

Selectivity:
• IC$_{50}$ of 10-100 nM against 8 of 282 human kinases
BRF113928: Study Design

- Single arm, phase 2, open label
- 70 sites among 11 countries

Dabrafenib 150 mg twice daily

Green-Dahlberg 2-stage design
H0: ORR ≤ 10% vs Ha: ORR ≥ 30%

NSCLC
BRAF V600E mutation
≥ 1 line prior tx

N = 20
Stage 1
Interim futility analysis
Stop for futility if < 3 responses out of first 20 patients

N = 20
Stage 2
Claim success if ≥ 8 responses out of first 40 patients

N = 20
Expansion

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a Six first line patients enrolled under protocol Amendment 07
b Expansion phase was added with protocol Amendment 07 to provide better precision of ORR estimate with total of 78 ≥ 2nd line patients enrolled to increase probability of at least 60 with BRAF V600E mutation centrally confirmed
BRF113928: Study Objectives

- **Primary objective**: Investigator-assessed ORR

- **Secondary objectives**: PFS, duration of response, overall survival (OS), safety, tolerability, and population pharmacokinetics

- **Analysis populations**:
  - Efficacy population (≥ 2nd line), N = 78
  - Safety population (All Treated), N = 84
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>≥ 2nd Line (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (range)</td>
<td>66 (28-85)</td>
</tr>
<tr>
<td>Sex, (%)</td>
<td>Female/male</td>
<td>39 (50)/39 (50)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>59 (76)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>17 (22)</td>
</tr>
<tr>
<td></td>
<td>African American</td>
<td>2 (3)</td>
</tr>
<tr>
<td>ECOG PS at baseline, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>16 (21)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>50 (64)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never smoked</td>
<td>29 (37)</td>
</tr>
<tr>
<td></td>
<td>Smoker ≤ 30 pack-years</td>
<td>25 (32)</td>
</tr>
<tr>
<td></td>
<td>Smoker &gt; 30 pack-years</td>
<td>24 (31)</td>
</tr>
<tr>
<td>Histology at initial diagnosis, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>75 (96)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Number of prior systemic regimens for metastatic disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>40 (51)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>14 (18)</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>24 (31)</td>
</tr>
<tr>
<td>Time since last progression, months (n = 71)</td>
<td>Median (range)</td>
<td>1.1 (0.2 – 6.8)</td>
</tr>
</tbody>
</table>
BRAF inhibitor phase 2 trial in NSCLC

<table>
<thead>
<tr>
<th>Best response</th>
<th>≥ 2nd Line (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR, n (%)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>SD&lt;sup&gt;b&lt;/sup&gt;, n (%)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>Not evaluable (NE), n (%)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Response rate (confirmed CR + PR)</td>
<td>32%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(21.9–43.6)</td>
</tr>
<tr>
<td>Disease control rate (CR + PR + SD)</td>
<td>56%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(44.7–67.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1st line subjects (n=6): 3=PR, 3=SD.

<sup>b</sup> SD is defined as meeting SD ≥ 12 weeks (planned time for the second post-baseline disease assessment).
BRAF inhibitor phase 2 trial in NSCLC

Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in ≥ 2nd Line (N = 78)

Median PFS\(^a\) months (95% CI) 5.5 (2.8 – 7.3)
Inhibition of BRAF by vemurafenib « relieves » a negative feedback loop that keeps EGFR inactive

Activated RAS causes resistance inducing RAF dimers formation

Janne, Nature 2012
Melanoma story: V600E BRAF and MEK dual inhibition

Altered non melanoma cell

Oncogenic RAS

RTK → RAS

WT BRAF

CRAF

MEK

ERK

Cell survival & proliferation

Dabrafenib

Vemurafenib

Trametinib

Cobimetinib

Melanoma cell

RTK → RAS

BRAF V600E

MEK

ERK

Cell survival & proliferation

Resistances:
- BRAF splice variant
- NRAS, MEK mutations
- COT…

Improved PFS
BRAF resistance mechanisms in NSCLC?

Molecular Characterization of Acquired Resistance to the BRAF Inhibitor Dabrafenib in a Patient with BRAF-Mutant Non–Small-Cell Lung Cancer

Charles M. Rudin, MD, PhD,* Kelvin Hong, MD,* and Michael Streit, MD†

**TABLE 1.** Tumor Mutational Profiles Pretreatment and upon Disease Progression

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prestudy*</th>
<th>Progressive Disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>V600E</td>
<td>V600E</td>
</tr>
<tr>
<td>CCND3</td>
<td>Amplification</td>
<td>Amplification</td>
</tr>
<tr>
<td>ARID1A</td>
<td>S90fs*11</td>
<td>S90fs*11</td>
</tr>
<tr>
<td>RB1</td>
<td>S807*</td>
<td>S807*</td>
</tr>
<tr>
<td>KRAS</td>
<td>—</td>
<td>G12D</td>
</tr>
<tr>
<td>TP53</td>
<td>—</td>
<td>R175H</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>—</td>
<td>R24fs*20</td>
</tr>
</tbody>
</table>

* Both tumor biopsies were profiled using the Foundation One next-generation sequencing assay.
BRAF resistance mechanisms in NSCLC?

• Activation of signalling through HER-3 as a mechanism of resistance/refractoriness to BRAFi/MEKi?

• HER-3 pathway activation observed in patients?

➢ Combination of MEK or BRAF TKI and a pan-HER TKI? What can we achieve in the clinic?
Conclusions (1)

BRAF mutated NSCLC represent small distinct subgroups of oncogene addicted cancers with specific demographics and potentially outcomes.

Prognostic feature BRAF mutations remain to be studied in large cohorts of patients.

We identified some men and heavy smokers (up to 60 packs-year) suggesting that and BRAF testing should not be restricted to clinically defined subgroups.

The targeted strategy against BRAF requires a prospective evaluation in large collaborative international clinical trials. BRAF non-V600E mutated NSCLC treatment remains to be explored.
Conclusions (2) BRAF trials

A Phase II Study of the BRAF Inhibitor Dabrafenib as a single-agent and in combination with the MEK Inhibitor Trametinib in ongoing in Subjects With BRAF V600E NSCLC (NCT01336634)

A Phase Ib/II, multicenter, open-label, dose escalation study of LGX818 in combination with MEK162 in patients with BRAF V600 - dependent advanced solid tumors (NCT01543698) is recruiting

BASKET study (NCT01524978) of Vemurafenib with expansion phase in NSCLC ongoing

Several early phase 1 trials including RTKi (EGFR, HER1-3, MET) and BRAF TKIs as well as intermittent schedules ongoing
Thanks for your attention