Session 2
Generating and interpreting data in rare subsets of common and uncommon cancers
Moderator: Gideon M Blumenthal, MD, CDER

Vignettes
• **Dominant oncogenic driver**: Lecia V Sequist, MD, MPH, Massachusetts General Hospital
• **Multiple oncogenic drivers**: Scott Kopetz, MD, PhD, University of Texas MD Anderson Cancer Center

Panel Discussion
• Rosane Charlab Orbach, PhD, CDER; Steven Lemery, MD, CDER; Barbara Conley, MD, NCI; Lecia Sequist, MD, MPH, Massachusetts General Hospital; Scott Kopetz, MD, PhD, University of Texas MD Anderson Cancer Center; Mary W Redman, PhD, Fred Hutchinson Cancer Research Center; Gregory Curt, MD, AstraZeneca
EGFR TKIs in NSCLC

Lecia V. Sequist, MD, MPH
Center for Thoracic Cancers, Mass General Hospital Cancer Center
Associate Professor of Medicine, Harvard Medical School
The history of EGFR in NSCLC

- 5/03: Gefitinib received conditional FDA approval for 3rd line NSCLC
- 4/04: EGFR mutations discovered - identifies oncogene-addicted biology that is exquisitely sensitive to EGFR TKIs
- 11/04: Erlotinib FDA approval (any NSCLC in 2nd line and beyond)
- 6/05: Gefitinib use restricted based on ISEL trial failing to meet OS endpoint
The history of EGFR in NSCLC

- 2008-12: Mounting data that pts benefiting most from EGFR TKIs are EGFR mutants
- 2011: NCCN guidelines recommend testing for EGFR mutations at the time of diagnosis
- 5/13: Erlotinib FDA approved in 1st line for del 19 and L858R EGFR mutants
- 7/13: Afatinib FDA approved in 1st line for del 19 and L858R EGFR mutants
Types of EGFR Mutations

Methods of testing can influence which mutations are identified.
Vignette: Afatinib
Lux-Lung 3 Study design

Stage IIIB (wet)/IV lung adenocarcinoma (AJCC version 6)

EGFR mutation in tumor (central lab testing; Therascreen EGFR29* RGQ PCR)

Randomization 2:1
Stratified by:
EGFR mutation (Del19/L858R/other)
Race (Asian/non-Asian)

Afatinib 40 mg/day

Cisplatin + pemetrexed
75 mg/m² + 500 mg/m²
i.v. every 21 days, up to 6 cycles

EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.

†217 independent events needed to detect HR of 0.64 (or median increase in PFS from 7 to 11 months) at two-sided 5% significance level with 90% power; ‡Tumor assessments: every 6 weeks until Week 48 and every 12 weeks thereafter until progression/start of new therapy; §Patient-reported outcomes: Q-5D, EORTC QLQ-C30 and QLQ-LC13 at randomization and every 3 weeks until progression or new anticancer therapy.
### Lux-Lung 3: Patient demographics/characteristics

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=230)</th>
<th>Cis/Pem (n=115)</th>
<th>Total (n=345)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (36)</td>
<td>38 (33)</td>
<td>121 (35)</td>
</tr>
<tr>
<td>Female</td>
<td>147 (64)</td>
<td>77 (67)</td>
<td>224 (65)</td>
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<tr>
<td><strong>Age, years, median (range)</strong></td>
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<tr>
<td></td>
<td>62 (28–86)</td>
<td>61 (31–83)</td>
<td>61 (28–86)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>61 (27)</td>
<td>30 (26)</td>
<td>91 (26)</td>
</tr>
<tr>
<td>Eastern Asian</td>
<td>165 (72)</td>
<td>83 (72)</td>
<td>248 (72)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1)</td>
<td>2 (2)</td>
<td>6 (2)</td>
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<tr>
<td><strong>Smoking status, n (%)</strong></td>
<td></td>
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<tr>
<td>Never smoked</td>
<td>155 (67)</td>
<td>81 (70)</td>
<td>236 (68)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>70 (30)</td>
<td>32 (28)</td>
<td>102 (30)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (2)</td>
<td>2 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>Stage (AJCC 6.0), n (%)</strong></td>
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<td></td>
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</tr>
<tr>
<td>IIIB (wet)</td>
<td>20 (9)</td>
<td>17 (15)</td>
<td>37 (11)</td>
</tr>
<tr>
<td>IV</td>
<td>210 (91)</td>
<td>98 (85)</td>
<td>308 (89)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>92 (40)</td>
<td>41 (36)</td>
<td>133 (39)</td>
</tr>
<tr>
<td>1</td>
<td>138 (60)</td>
<td>73 (64)</td>
<td>211 (61)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>EGFR mutation, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del19</td>
<td>113 (49)</td>
<td>57 (49)</td>
<td>170 (49)</td>
</tr>
<tr>
<td>L858R</td>
<td>91 (40)</td>
<td>47 (41)</td>
<td>138 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (11)</td>
<td>11 (10)</td>
<td>37 (11)</td>
</tr>
</tbody>
</table>
LUX-Lung 3: PFS in all patients

Sequist et al, JCO 2013
LUX-Lung 3: PFS in those with common mutations

Sequist et al, JCO 2013
FDA Approval was for “common mutations” only

GILOTRIF™ (afatinib) tablets, for oral use
Initial U.S. Approval: 2013

INDICATIONS AND USAGE
GILOTRIF is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (1).

Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations (1).
Activity of afatinib in uncommon epidermal growth factor receptor (EGFR) mutations: Findings from three prospective trials of afatinib in EGFR mutation-positive lung cancer

J. C.-H. Yang¹, L.V. Sequist², S. L. Geater³, C.-M. Tsai⁴, T. Mok⁵, M. H. Schuler⁶, N. Yamamoto⁷, D. Massey⁸, V. Zazulina⁸, Yi-Long Wu⁹

¹National Taiwan University Hospital, Taipei, Taiwan; ²Massachusetts General Hospital, Boston, MA, USA; ³Division of Respiratory and Respiratory Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand; ⁴Taipei Veterans General Hospital, Taipei, Taiwan; ⁵The Chinese University of Hong Kong, Hong Kong; ⁶West German Cancer Center, University Duisburg-Essen, Essen, Germany; ⁷Shizuoka Cancer Center, Shizuoka, Japan; ⁸Boehringer Ingelheim Limited, Bracknell, UK; ⁹Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China
*EGFR mutations detected by TheraScreen EGFR29 test:

- Common: 19 deletions in exon 19 and L858R in exon 21
EGFR mutation-positive patients in LUX-Lung trials

**LUX-Lung 2**
- Phase II
- N=129
- Del19: n=408
  - n=52
- L858R: n=330
  - n=54
- Uncommon: n=100
  - n=23

**LUX-Lung 3**
- Phase III
- N=345
- Del19: n=408
  - n=170
- L858R: n=330
  - n=138
- Uncommon: n=100
  - n=37

**LUX-Lung 6**
- Phase III
- N=364
- Del19: n=408
  - n=186
- L858R: n=330
  - n=138
- Uncommon: n=100
  - n=40

Patients with uncommon mutations treated with afatinib
- n=23
- n=26
- n=26
Baseline patient characteristics across mutation types

<table>
<thead>
<tr>
<th></th>
<th>Del 19 n=408</th>
<th>L858R n=330</th>
<th>Uncommon n=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years median (range)</td>
<td>58 (27–84)</td>
<td>61 (32–86)</td>
<td>60 (30–86)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>256 (63)</td>
<td>223 (68)</td>
<td>58 (58)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>288 (71)</td>
<td>242 (73)</td>
<td>68 (68)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>98 (24)</td>
<td>75 (23)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22 (5)</td>
<td>13 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>54 (13)</td>
<td>39 (12)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Asian</td>
<td>351 (86)</td>
<td>289 (88)</td>
<td>85 (85)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Stage (AJCC 6.0), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB (wet)</td>
<td>33 (8)</td>
<td>31 (9)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>IV</td>
<td>375 (92)</td>
<td>299 (91)</td>
<td>97 (97)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>150 (37)</td>
<td>112 (34)</td>
<td>43 (43)</td>
</tr>
<tr>
<td>1</td>
<td>257 (63)</td>
<td>214 (65)</td>
<td>57 (57)</td>
</tr>
<tr>
<td>2</td>
<td>1 (&lt;1)</td>
<td>4 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status.
## Subgroups of patients with uncommon mutations

<table>
<thead>
<tr>
<th>Categories</th>
<th>De novo T790M</th>
<th>Exon 20 insertions</th>
<th>Other (exon 18, 19, 20, 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>14</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>Mutations (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T790M alone (3)</td>
<td></td>
<td></td>
<td>L861Q alone (12)</td>
</tr>
<tr>
<td>T790M+Del19 (3)</td>
<td></td>
<td></td>
<td>G719X alone (8)</td>
</tr>
<tr>
<td>T790M+L858R (6)</td>
<td></td>
<td></td>
<td>G719X+S768I (5)</td>
</tr>
<tr>
<td>T790M+G719X (1)</td>
<td></td>
<td></td>
<td>G719X+L861Q (3)</td>
</tr>
<tr>
<td>T790M+L858R+G719X</td>
<td></td>
<td></td>
<td>E709G or V+L858R (2)</td>
</tr>
<tr>
<td></td>
<td>n/a</td>
<td></td>
<td>S768I+L858R (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S768I alone (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L861P alone (1)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>P848L alone (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R776H+L858R (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L861Q+Del19 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>K739_1744dup6 (1)</td>
</tr>
</tbody>
</table>
## Objective response and disease control rates

### Independent review

<table>
<thead>
<tr>
<th></th>
<th>De novo T790M n=14</th>
<th>Exon 20 insertions n=23</th>
<th>Other n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate (CR + PR), n (%)</strong></td>
<td>2 (14.3%)</td>
<td>2 (8.7%)</td>
<td>27 (71.1%)</td>
</tr>
<tr>
<td><strong>Median duration of response, months (range)</strong></td>
<td>8.2 (4.1–12.4)</td>
<td>7.1 (4.2–10.1)</td>
<td>11.1 (1.3–35.0+)</td>
</tr>
<tr>
<td><strong>Disease control rate (CR + PR + SD), n (%)</strong></td>
<td>9 (64.3%)</td>
<td>15 (65.2%)</td>
<td>32 (84.2%)</td>
</tr>
</tbody>
</table>

+Patient data censored
Tumour shrinkage in patients with uncommon mutations

Independent review (n=67†)

- **De novo T790M (n=14):**

- **Exon 20 insertions (n=20)**

- **Other (n=33):**

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*8 patients were not included due to insufficient data
## Progression-free survival and overall survival in patients

<table>
<thead>
<tr>
<th></th>
<th>De novo T790M n=14</th>
<th>Exon 20 insertions n=23</th>
<th>Other n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (range)</td>
<td>2.9 (0.3–13.8)</td>
<td>2.7 (0.4–11.9)</td>
<td>10.7 (0.0–35.8+)</td>
</tr>
<tr>
<td>Median OS, months (range)</td>
<td>14.9 (1.5–30.5)</td>
<td>9.4 (0.4–32.2+)</td>
<td>18.6 (0.0–51.3+)</td>
</tr>
</tbody>
</table>

*Patient data censored; NE = not estimable*
# Activity of afatinib in specific uncommon EGFR mutations

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>ORR, n (%)</th>
<th>PFS (months), median (95% CI)</th>
<th>OS (months), median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G719X</strong>&lt;br&gt;(n=18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X (n=8)</td>
<td>14 (78)</td>
<td>13.8 (6.8–NE)</td>
<td>26.9 (16.4–NE)</td>
</tr>
<tr>
<td>G719X+T790M (n=1)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>G719X+S768I (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G719X+L861Q (n=3)</td>
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</tr>
<tr>
<td>G719X+T790M+L858R (n=1)</td>
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</tr>
<tr>
<td><strong>L861Q</strong>&lt;br&gt;(n=16)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>L861Q (n=12)</td>
<td>9 (56)</td>
<td>8.2 (4.5–16.6)</td>
<td>16.9 (15.3–22.0)</td>
</tr>
<tr>
<td>L861Q+G719X (n=3)</td>
<td></td>
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<td></td>
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<tr>
<td>L861Q+Del19 (n=1)</td>
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<tr>
<td><strong>S768I</strong>&lt;br&gt;(n=8)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>S768I (n=1)</td>
<td>8 (100)</td>
<td>14.7 (2.6–NE)</td>
<td>NE (3.4–NE)</td>
</tr>
<tr>
<td>S768I + G719X (n=5)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>S768I +L858R (n=2)</td>
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</tr>
</tbody>
</table>

Note: A patient may be presented in more than one category

NE = not estimable
Summary

- Largest prospective dataset in patients with uncommon EGFR mutations (n=75)
- High heterogeneity within the subgroup with uncommon EGFR mutations
- Low response rate in patients with exon 20 insertions and T790M tumours
  - Durable tumour control observed in some cases (PFS up to 13.8 months)
- Activity was observed in other exon 18 (G719X), 20 (S768I) and 21 (L861Q) mutations that are known to be less responsive to reversible EGFR TKIs
  - Activity was in the range of efficacy observed with afatinib in common EGFR mutations
Questions to consider

• EGFR mutations have changed the paradigm for lung cancer therapy in many ways
  – Genotype-directed therapy is now a well-established paradigm
  – Physicians and patients are much more likely to pursue biopsies

• How to make treatment decisions for rare subsets of EGFR is less clear

• Given the data I’ve shown you, I feel comfortable prescribing afatinib for G719, L861 and S786 mutants… but is it enough to change the label??
Patient-derived models of acquired resistance can identify effective drug combinations for cancer

Adam S. Crystal,1 Alice T. Shaw,1 Lecia V. Sequist,1 Luc Friboulet,1 Matthew J. Niederst,1 Elizabeth L. Lockerman,1 Rosa L. Frias,1 Justin F. Gainor,1 Arnaud Amzallag,1 Patricia Greninger,1 Dana Lee,1 Anuj Kalsy,1 Maria Gomez-Caraballo,1 Leila Elamine,1 Emily Howe,1 Wooyoung Hur,3 Eugene Lifshits,1 Hayley E. Robinson,2 Ryohei Katayama,1 Anthony C. Faber,1 Mark M. Awad,1 Sridhar Ramaswamy,1 Mari Mino-Kenudson,2 A. John Iafrate,2 Cyril H. Benes,1* Jeffrey A. Engelmann1*
Studies of Acquired TKI Resistance

Cell lines

- **Sensitive**
- **Resistant**

Increasing TKI dose

Mice

- **Sensitive**
- **TKI**
- **TKI**
- **Resistant**

Patients

- **Sensitive**
- **TKI**
- **TKI**
- **Resistant**

Repeat Biopsy
Ex-vivo drug combination screen

A

Sensitive

Downstream signaling

Survival

Cell death

Resistant

Downstream signaling

Survival

Survival

Cell death

B

MISS

HIT

Cell viability

log[ABT263], μM

log[KIN001-113], μM

Single Agent

Combination
Summary of results from Crystal, et al

- This method independently (unbiased) confirmed known mechanisms of resistance in cell line models
- Novel mechanisms of resistance were uncovered, along with “built-in” treatment strategies
  - FGFR3 mutation in one EGFR mutant pt with AR to afat/cetux
  - MEK activation in one ALK patient with AR to ceritinib
  - Several ALK patients had increased SRC signaling and 5 of 5 tested models showed successful response to Alk + Src inhibition
Acknowledgments

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- Anna Farago
- Jennifer Logan
- Ally Wanat
- Lisa Stober
- Beth Kennedy
- Jennifer Nunes
- Mike Lanuti
- John Wain
- Subba Digumarthy
- Kate Schultz
- Joe Gurski

**Engelman Lab**
- Matt Niederest
- Adam Crystal
- Aaron Hata

**MGH Pathology**
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- Mari Mino-Kenudson
- Dora Dias-Santagata

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- Shannon Stott
- James Sullivan
- Mike Rothenberg

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- Teresa Moran

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- Heather Wakelee

**National Taiwan University**
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- Sarah Goldberg

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- Belinda Waltman

**Funding**
- Uniting Against Lung Cancer
- NIH/NCI (R21CA156000)
- LunGevity
- DOD
Multiple Oncogenic Drivers: BRAF mutant Colorectal Cancer

Scott Kopetz, MD, PhD.
Department of GI Medical Oncology
MD Anderson Cancer Center
Why BRAF in CRC provides an example for discussion

- Defines a unique molecular AND clinical subset
  - Substantial clinical need
- **Compensatory response** uncovers multiple key drivers: BRAF and EGFR most prominent
- **Proof of concept** being established
  - In other tumor types… to a degree
  - With strong preclinical rationale established
  - In multiple single arm studies
  - In randomized CRC trials with most common mutation
    - With considerable screening effort
- **Extension to rare(r) variants discussed**
Serrated Adenoma / $\text{BRAF}^{\text{mut}}$ Subgroup

- BRAF mutations reflect a unique subset of CRC
  - Distinct molecular biology
  - Unique precursor lesion and metastasis pattern
  - Poor outcomes with standard-of-care

- **5% prevalence in metastatic disease**
Unique BRAF\textsuperscript{mut} Clinical Behavior

Atypical patterns of metastases

- Liver: P<0.05
- Lung: P<0.05
- Peritoneum: P<0.05
- Distant LNs: P<0.05
- Brain: P<0.05

- Increased incidence compared to BRAF wild type

Very short overall survival

- Hazard Ratio of 10.6 for OS
- Less than 1 year OS

Morris et al., Clin Colorectal Cancer ‘13
Tran, Kopetz, et al, Cancer 2011
Limited Benefit of Standard of Care for BRAF$^{\text{mut}}$ CRC Patients

All comers

![Bar graph showing PFS (months) for different lines of treatment for all comers.]

BRAF mutation

![Bar graph showing PFS (months) for different lines of treatment for BRAF mutation patients.]

Progression at First Restaging

Morris, et al Clin Colorectal Cancer, in press
BRAF mutations define a unique subtype by gene expression

- BRAF mutations
- Hypermethylation
- Microsatellite instability
- Limited chromosomal instability

N=4,500 patients
Presented by:
Dienstmann, ASCO '14
How to treat these patients?

BRAF inhibitor

BRAF mutation
Vemurafenib (PLX4032)

%Change From Baseline (Sum of Lesion Size)

81% Response Rate

5% Response Rate

Refractory Melanoma

Refractory Colorectal

Same mutation, same inhibitor..... Different molecular context

A cautionary tale for bridging between tumor types
The vision of molecular oncology 10 years ago....
BRAF inhibition seemed to be necessary but not sufficient.....

Prompting a hunt for agents for combination
Minimal Improved Efficacy with Dual BRAF + MEK Inhibition

BRAF inhibition

5% Response Rate

%Change From Baseline (Sum of Lesion Size)

-100
-75
-50
-25
0
25
50
75
100

Vemurafenib

BRAF + MEK inhibition

12% Response Rate

GSK212 + GSK436

Corcoran et al ASCO '12, Kopetz et al ASCO '10
Critical Finding: EGFR Identified in Synthetic Lethality Screen

Unbiased screen of kinome library

Prahallad et al. Nature '12
Critical Finding: Feedback EGFR Signaling

Prahallad et al. Nature '12
Critical Finding: Feedback EGFR Signaling

Confirmation: Replication of Findings

Prahallad et al Nature ’12
Synergy in Murine Models: 
BRAF + EGFR

Cell line and Patient-derived xenograft models

Kopetz, unpublished; Yang et al Can Res ‘11

Prahallad et al Nature ’12; Corcoran et al Can Disc ‘12
Clinical Efforts in BRAF\textsuperscript{mut}

- BRAFi+ EGFRi
  - BRAFi+ EGFRi + PI3Ki
    - Novartis
  - BRAFi+ EGFRi + MEK\textsubscript{i}
    - Roche/Genentech
    - GSK
  - BRAFi+ EGFRi + chemo
    - US Cooperative Groups

Roche/Genentech

GSK
Vemurafenib + Cetuximab Regimen

Historical response rate is <10% for cetuximab and irinotecan, with PFS of 2.4 months for BRAF<sup>mut</sup>
GSK: Dabrafenib + Panitumumab + Trametinib

BRAF + MEK + EGFR inhibition

6/15 = 40%
SD=80%

Bendell et al ASCO ‘14
Future Clinical Efforts in $\text{BRAF}^{\text{mut}}$

- BRAFi + EGFRi
  - BRAFi + EGFRi + PI3Ki (Roche/Genentech)
  - BRAFi + EGFRi + MEKi (GSK)
  - BRAFi + EGFRi + chemo (US Cooperative Groups)

- BRAFi + EGFRi (Novartis)
## Summary of preliminary activity in studies of BRAFi-based therapy in BRAFmut CRC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pathway</th>
<th>PR/C R</th>
<th>SD</th>
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<tr>
<td>D + T</td>
<td>BRAF+MEK</td>
<td>12%</td>
<td>51%</td>
<td>63%</td>
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<tr>
<td>E + C</td>
<td>BRAF+EGFR</td>
<td>29.2%</td>
<td>50%</td>
<td>79.2%</td>
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<td>D + T + P</td>
<td>BRAF+MEK+EGFR</td>
<td>40%</td>
<td>40%</td>
<td>80%</td>
<td>FOCUS4</td>
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<tr>
<td>V + C + Ir</td>
<td>BRAF+EGFR+chemo</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
<td>SWOG RPh2</td>
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<tr>
<td>E + C + BYL</td>
<td>BRAF+EGFR+PI3K</td>
<td>30%</td>
<td>60%</td>
<td>90%</td>
<td>None</td>
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</table>

D = dabrafenib, T = trametinib, P = panitumumab, V = vemurafenib, C = cetuximab, E = encorafenib, Ir = irinotecan, BYL = BYL719
SWOG 1406: BRAF + EGFR

Eligibility:
1) BRAF V600 mutation
2) Prior treatment for metastatic disease
3) No more than 2 prior progression on chemotherapy
4) No prior cetuximab

Stratified:
1) Prior treatment with irinotecan

BRAF V600E mutation only
Primary Endpoint: PFS
N=78 treated patients

Screening 1,500 patients

HR 0.5, 80% power, two-sided alpha 0.05

Kopetz, PI; Enrolling
Generation of Patient-Derived Xenograft Models in BRAF$^{\text{mut}}$ Trials: *Tools to ask the next questions*

Atreya, Corcoran, Kopetz  ASCO ‘14
Leveraging PDX Co-Clinical Models

• **Understanding…**
  – Mechanisms of Acquired Resistance
  – Mechanisms of Innate resistance

• **Pharmacodynamics**

• Evaluate combination in pts receiving control arm
  – Increasing knowledge from a small studies

• With validation, can be used as controlled n=1 studies for combinations
  – Patient responds to Novel + Novel… what activity would have been seen in this patient for each single agent
Pharmacodynamic Bridging Would Have Identified Differences in CRC and Melanoma

Colorectal Cancer

BRAF/MEK only

BRAF/MEK + EGFR

Melanoma

BRAF only

Bendell et al ASCO ‘14
What about mutations other than BRAF V600E?
## Diversity of BRAF mutations

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### ACTIVATING

- 466: G466V (1)
- 466: G466E (1, 6)
- 466: G466R (6)
- 472: Y472C (4)
- 590: V590I (14)
- 594: D594V (1, 6)
- 594: D594G (5)
- 596: G596R (1)
- 596: G596V (9)
Larger number of VUS....

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References

4. johnson F et al., (2011) unpub results
Rare BRAF VUS
VUS Interrogation for Multiple Drivers

Single and Multiple Drivers

- Ability to activate MAPK signaling
- Inhibited with agent

Multiple Drivers

- Feedback network in place
- Some measure of combination benefit
Why BRAF in CRC provides an example for discussion

- Defines a unique molecular AND clinical subset
  - Substantial clinical need
- Compensatory activity uncovers at least two key drivers: BRAF and EGFR
- Proof of concept being established
  - In other tumor types... to a degree
  - With strong preclinical rationale established
  - In multiple single arm studies
  - In randomized CRC trials with most common mutation
    - With considerable screening effort
- Extension to other rare(r) mutations discussed
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