Advances in Targeted Therapy for Lung Cancer

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Disclosures

- Consultant
  - Amgen
  - Ariad
  - Astellas
  - Euclises
  - Nektar

- Research support (to institution)
  - Ariad, Bristol Myers Squibb, Boehringer Ingelheim, Clovis, Eisai, Novartis, Pfizer, Xcovery, Adaptimmune, Medimmune, Stemcentrx
BACKGROUND
Evolution of NSCLC subtyping from histologic to molecular based

Li T et al. JCO 2013;31:1039-1049
Driver Mutation Incidence In Lung Cancers

- Unknown: 35%
- KRAS Mutation: 18%
- PTEN Loss: 1%
- BRAF Mutation: 3%
- ROS1 Fusion: 2%
- EGFR Mutation: 1%
- MET Amplification: 1%
- RET Fusion: 1%
- PIK3CA Mutation: 1%
- DDR2 Mutation: 1%
- AKT Mutation: 1%
- Double Mutations: 1%
- HER2 Mutation: 1%
- ALK Fusion: 1%
## Oncogene mutations and therapeutic options

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Mutation prevalence</th>
<th>Therapy</th>
<th>Predicted response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR</strong></td>
<td>Asians 30-40%/Caucasian 10-20%</td>
<td>EGFR TKIs (most mutations)/pan-HER inhibitors</td>
<td>Erlotinib 60-80% Gefitinib 70% Afatinib 60% Osimertinib 50-60% (T790M)</td>
</tr>
<tr>
<td><strong>ALK</strong></td>
<td>1-7%</td>
<td>ALK inhibitors/HSP90 inhibitors</td>
<td>Crizotinib 50-60% Ceritinib 60% Alectinib 60%</td>
</tr>
<tr>
<td><strong>KRAS</strong></td>
<td>Asians 10%/Caucasian 30%</td>
<td>possible MEK inhibition; CDK4/6 inhibition</td>
<td>NA</td>
</tr>
<tr>
<td><strong>ROS1</strong></td>
<td>1.7%, higher in Asians</td>
<td>ALK inhibitors</td>
<td>Crizotinib 60-70%</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>2%</td>
<td>Trastuzumab; pan-HER inhibitors</td>
<td>Dacomitinib 12%</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>1.7% (15% in EGFR/ALK/KRAS-)</td>
<td>RET inhibitors</td>
<td>Cabozantinib 40%</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>2%</td>
<td>BRAF/MEK inhibitors</td>
<td>Dabrafenib 30% Dabraf/tremetinib 60%</td>
</tr>
<tr>
<td><strong>MET</strong></td>
<td>10%</td>
<td>Crizotinib/MET inhibitors</td>
<td>25%</td>
</tr>
<tr>
<td><strong>NTRK</strong></td>
<td>0.1%</td>
<td>Crizotinib/NTRK inhibitors</td>
<td>NA</td>
</tr>
</tbody>
</table>
Why Does Testing Matter? Survival by Use of Targeted Therapy

<table>
<thead>
<tr>
<th>Genotype/Therapy</th>
<th>Median OS, y</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologic driver + targeted therapy</td>
<td>3.49</td>
<td>3.02-4.33</td>
</tr>
<tr>
<td>Oncologic driver + no targeted therapy</td>
<td>2.38</td>
<td>1.81-2.93</td>
</tr>
<tr>
<td>No targeted therapy</td>
<td>2.08</td>
<td>1.84-2.46</td>
</tr>
</tbody>
</table>

Kris et al, 2014.
TARGETING EGFR—FIRST LINE
IPASS: PFS by EGFR Mutation Status

- Randomized phase III trial; previously untreated pts with advanced NSCLC (N = 1217)
- PFS: gefitinib superior to carboplatin/paclitaxel in ITT population
- EGFR mutations strongly predicted PFS (and tumor response) to first-line gefitinib vs carboplatin/paclitaxel

**EGFR Mutation Positive**

- HR: 0.48 (95% CI: 0.36-0.64; P < .001)

**EGFR Mutation Negative**

- HR: 2.85 (95% CI: 2.05-3.98; P < .001)

### Randomized Studies of First-Line EGFR TKIs in Patients With *EGFR* Mutations

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Agent</th>
<th>N (EGFR mut +)</th>
<th>RR</th>
<th>Median PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mok et al</td>
<td>IPASS</td>
<td>Gefitinib</td>
<td>261</td>
<td>71.2% vs 47.3%</td>
<td>9.8 vs 6.4</td>
<td>21.6 vs 21.9</td>
</tr>
<tr>
<td>Han et al</td>
<td>First-SIGNAL</td>
<td>Gefitinib</td>
<td>42</td>
<td>84.6% vs 37.5%</td>
<td>8.0 vs 6.3</td>
<td>27.2 vs 25.6</td>
</tr>
<tr>
<td>Mitsudomi et al</td>
<td>WJTOG 3405</td>
<td>Gefitinib</td>
<td>172</td>
<td>62.1% vs 32.2%</td>
<td>9.2 vs 6.3</td>
<td>30.9 vs NR</td>
</tr>
<tr>
<td>Maemondo et al</td>
<td>NEJGSG002</td>
<td>Gefitinib</td>
<td>230</td>
<td>73.7% vs 30.7%</td>
<td>10.8 vs 5.4</td>
<td>30.5 vs 23.6</td>
</tr>
<tr>
<td>Zhou et al</td>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>154</td>
<td>83% vs 36%</td>
<td>13.7 vs 4.6</td>
<td>22.7 vs 28.9</td>
</tr>
<tr>
<td>Rosell et al</td>
<td>EURTAC</td>
<td>Erlotinib</td>
<td>174</td>
<td>58% vs 15%</td>
<td>9.7 vs 5.2</td>
<td>19.3 vs 19.5</td>
</tr>
<tr>
<td>Sequist et al</td>
<td>LUX-Lung 3</td>
<td>Afatinib</td>
<td>345</td>
<td>56% vs 23%</td>
<td>13.6 vs 6.9</td>
<td>30.3 vs 26.2</td>
</tr>
<tr>
<td>Wu et al</td>
<td>LUX-Lung 6</td>
<td>Afatinib</td>
<td>364</td>
<td>67% vs 23%</td>
<td>11.0 vs 5.6</td>
<td>22.1 vs 22.2</td>
</tr>
</tbody>
</table>

Crossover to an EGFR TKI in the control group reduces any chance of an OS benefit

EGFR, epidermal growth factor receptor; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.

## EGFR TKIs approved or in development

<table>
<thead>
<tr>
<th>Drug</th>
<th>EGFR L858R</th>
<th>EGFR Exon 19 del</th>
<th>EGFR T790M</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><strong>1st gen</strong></em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gefitinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>erlotinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>icotinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>afatinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>dacomitinib</em></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>neratinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em><strong>2nd gen</strong></em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>osimertinib (AZD9291)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>rociletinib (CO1686)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em><strong>3rd gen</strong></em></td>
<td></td>
<td></td>
<td>ALK</td>
</tr>
<tr>
<td>EGF 816</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ASP8273</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BI1482694</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>AP26113</td>
<td>+</td>
<td>+</td>
<td>ALK</td>
</tr>
</tbody>
</table>
Overall Survival (OS) in LUX-Lung 3 & 6

- Stage IIIIB/IV adenocarcinoma of the lung
- Presence of EGFR mutation in the tumor tissue*
- No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization 2:1

Stratification by EGFR mutation type:
Del19/L858R/other
& by race (LUX-Lung 3 only): Asian/non-Asian

Afatinib 40 mg orally once daily

LUX-Lung 3:
Cisplatin + pemetrexed up to 6 cycles

LUX-Lung 6:
Cisplatin + gemcitabine up to 6 cycles

Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, OS, PRO, safety

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

Combined OS analysis: Mutation Categories

Del19
- Afatinib: Median, months 31.7
- Chemo: Median, months 20.7
- HR: 0.59 (0.45–0.77), p=0.0001

L858R
- Afatinib: Median, months 22.1
- Chemo: Median, months 26.9
- HR: 1.25 (0.92–1.71), p=0.1600

Multi-study Comparison of PFS & OS in Del19 & L858R cancers in randomized trials

## Comparative Toxicity

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 3 Afatinib n=229</th>
<th>EURTAC(^1) Erlotinib n=84</th>
<th>IPASS(^2) Gefitinib n=607</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Grade ≥3</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14.8</td>
<td>5</td>
<td>3.8</td>
</tr>
<tr>
<td>Rash/acne(^*)</td>
<td>16.2</td>
<td>13</td>
<td>3.1</td>
</tr>
<tr>
<td>Stomatitis/mucositis(^*)</td>
<td>8.7</td>
<td>NR</td>
<td>0.2</td>
</tr>
<tr>
<td>Paronychia</td>
<td>11.4</td>
<td>NR</td>
<td>0.3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4.4</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>Fatigue(^*)</td>
<td>3.1</td>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.4</td>
<td>NR</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\(^*\)Group term at least in one of the trials included in the table

NR: not reported
Direct Comparisons of EGFR TKIs—Ongoing Phase III Trials

EGFR-mutated untreated

ARCHER 1050
Dacomitinib vs Gefitinib
N=440
OS

EGFR-mutated untreated

LUX Lung 7
Afatinib vs Gefitinib
N=316
PFS/OS

EGFR-mutated untreated

FLAURA
AZD9291 vs Erlotinib/Gefitinib
N=650
PFS
LUX-Lung 7—Afatinib vs. Gefitinib

Study design

- Stage IIIB/IV adenocarcinoma of the lung
- EGFR mutation (Del19 and/or L858R) in the tumor tissue*
- No prior treatment for advanced/metastatic disease
- ECOG PS 0/1

1:1

Afatinib 40 mg once daily†

Stratified by
- Mutation type (Del19/L858R)
- Brain metastases (present/absent)

Primary endpoints:
- PFS (independent)
- TTF
- OS

Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Duration of disease control
- Tumor shrinkage
- HRQoL
- Safety

Gefitinib 250 mg once daily

- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

*Central or local test
†Dose modification to 50, 30, 20 mg permitted in line with prescribing information

ECOG PS, Eastern Oncology Cooperative Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTF, time to treatment failure
LUX-Lung 7—Afatinib vs. Gefitinib

PFS by independent review

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>11.0</td>
<td>10.9</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.57–0.95)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0165</td>
<td></td>
</tr>
</tbody>
</table>

No. of patients

<table>
<thead>
<tr>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>159</td>
</tr>
</tbody>
</table>

Park K et al. Lancet Oncol 2016
LUX-Lung 7—Afatinib vs. Gefitinib

Drug-related AEs leading to discontinuation in >1 patient

- Diarrhea: Afatinib 5 (3.1%), Gefitinib 0%
- Fatigue*: Afatinib 0%, Gefitinib 2 (1.3%)
- Toxic skin eruption: Afatinib 0%, Gefitinib 2 (1.3%)
- ALT increase: Afatinib 0%, Gefitinib 5 (3.1%)
- AST increase: Afatinib 0%, Gefitinib 3 (1.9%)
- ILD: Afatinib 0%, Gefitinib 4 (2.5%)

*Grouped terms of AEs

Park K et al. Lancet Oncol 2016
Erlotinib vs Erlotinib + Bevacizumab in EGFR Mutant NSCLC (Phase II)

- NSCLC with sensitive EGFR mutations
- Stage IIIb/IV
- No prior chemo.
- PS 0-1

Primary endpoint
- PFS
- OS
- Response
- Side-effects
- Symptoms

Erlotinib n = 75

Erlotinib + Bev n = 75

• The sample size was calculated to be 150 in total (alpha = 0.2, power = .80) to confirm the superiority of Arm A (hazard ratio = 0.79).

Seto M et al; Lancet Oncol 2014: 15:1236
Erlotinib vs Erlotinib + Bevacizumab in EGFR Mutant NSCLC (PFS/OS)

Seto M et al; Lancet Oncol 2014: 15:1236
TARGETING ALK
Timeline: ALK-Fusion in NSCLC

EML4-ALK chromosomal rearrangements reported in NSCLC[1]

2007

Crizotinib antitumor activity in advanced cancers with EML4-ALK rearrangement[4]

2009

FDA approves crizotinib for treatment of ALK+ NSCLC[6]

2011

Preclinical studies document antitumor activity of ALK inhibitors in lung cancer cell lines and xenografts[2,3]

2008

Crizotinib produces a response in 47/82 ALK+ patients and a 6-mo PFS of 72%[5]

2010

**EML4/ALK Translocations**

- Typical phenotype
  - Young, male or female, never/scant smokers
  - Adenocarcinoma ± signet ring morphology
  - Poor response to EGFR TKI; conventional response to standard chemotherapy
  - No overlap with EGFR mutation genotype

---

**Crizotinib in ALK-Positive NSCLC (N = 143)**

MORE TARGETS
**ROS1 Rearrangements in NSCLC**

- First discovered in NSCLC in 2007
- Also found in some GBMs, cholangiocarcinomas, and other tumor types
- Activated by chromosomal rearrangement, leading to constitutive kinase activation and oncogene addiction
- No overlap with ALK

Summary of ROS1 Anti-Tumor Efficacy in PROFILE 1001 Study

Median PFS 19.2 months (95% CI, 14.4 to NR)

Dabrafenib/Trametinib in \textit{BRAF} mutated NSCLC

- ORR = 63\% and DCR = 88\% for dabrafenib plus trametinib\textsuperscript{1}
- ORR = 32\% and DCR = 56\% for dabrafenib as monotherapy\textsuperscript{2}

\textsuperscript{1} Johnson B WCLC 2015; \textsuperscript{2} Planchard Lancet Oncol 2016

*1 patient discontinued at day 23 and did not have any post-baseline scans for efficacy.

Images courtesy of B. Johnson et al, Dana-Farber - Boston
All patients develop resistance

Camidge et al., Lancet Onc 2012
EGFR RESISTANCE
Mechanisms of therapeutic resistance to kinase inhibitors

Primary resistance
- Tumor-intrinsic factors
  - Coexistent genetic alterations in the drug target
  - Coexistent mutations in other signaling genes
  - Inactivation of proapoptotic pathways
- Patient-specific factors
  - Plasma drug levels
  - Drug-drug interactions

Acquired resistance
- Target modification
  - Target gene amplification
  - "Second site" mutation within the target gene
  - Alternative splicing of the target gene
- Bypass signaling
  - Activation of "compensatory loops" to circumvent the inhibited target
- Histologic transformation
  - Epithelial-to-mesenchymal transition
  - Phenotypic change from NSCLC to SCLC
- Other mechanisms
  - Increased growth factor production

Examples of strategies to overcome acquired resistance
- Alternative dose or schedule
- Next-generation inhibitors
- Dual-target blockade
- Drug combinations
Relative frequencies of mechanisms of EGFR TKI acquired resistance

- T790M: 60%
- Unknown: 18%
- HER2: 8%
- HER2 + T790M: 4%
- Small cell + MET: 1%
- Small cell + T790M: 2%
- MET amplification: 3%
- MET + T790M: 3%

Mechanisms of Acquired Resistance to EGFR TKI therapy

<table>
<thead>
<tr>
<th>Secondary mutations</th>
<th>Alternative pathways</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR T790M</td>
<td>HER2 amplification</td>
<td>PD-L1</td>
</tr>
<tr>
<td>EGFR L844V</td>
<td>MET amplification</td>
<td>EMT</td>
</tr>
<tr>
<td>EGFR L718Q</td>
<td>mTORC1</td>
<td>Small cell transformation</td>
</tr>
<tr>
<td>EGFR C797S</td>
<td>AXL</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>EGFR D761Y</td>
<td>IGF1R</td>
<td></td>
</tr>
<tr>
<td>EGFR T854A</td>
<td>FGFR</td>
<td></td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>STAT3</td>
<td></td>
</tr>
<tr>
<td>NRAS mutation</td>
<td>PI3K</td>
<td></td>
</tr>
</tbody>
</table>
Response to Osimertinib (AZD9291)

Therapy for *EGFR* + resistant NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>RR T790M +</th>
<th>RR T790M -</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib/Cetux</td>
<td>35%</td>
<td>28%</td>
<td>4.7 mo</td>
</tr>
<tr>
<td>CO-1686</td>
<td>58%</td>
<td>ND</td>
<td>increased</td>
</tr>
<tr>
<td>AZD 9291</td>
<td>65%</td>
<td>22%</td>
<td>increased</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3 toxicity</th>
<th>Rash</th>
<th>Diarrhea</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib/Cetux</td>
<td>97%</td>
<td>71%</td>
<td>ND</td>
</tr>
<tr>
<td>CO-1686</td>
<td>4%</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>AZD 9291</td>
<td>27%</td>
<td>20%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Best timing for T790M inhibition?

Is it best to address T790M at time of clinical resistance or early on (at baseline or through serial plasma monitoring)?

adapted from T MOK
Detectable T790M at Baseline is Associated with a Worse PFS

Maheswaran and Sequist et al NEJM 2009
AURA Phase I dose escalation/expansion: study design

First-line cohort objective

Safety and tolerability of osimertinib (80 mg or 160 mg qd orally) as first-line therapy for patients with EGFRm advanced NSCLC

Key inclusion criteria:
- Aged ≥18 (≥20 in Japan)
- Locally advanced or metastatic NSCLC
- No prior therapy for advanced disease
- Measurable disease at baseline
- Patients must have EGFR mutation positive NSCLC (local test)

Key exclusion criteria:
- Prior history of ILD
- Symptomatic brain metastases

Data cut-off: 4 January 2016
Data from cohorts in grayed out boxes are not included in the analyses reported here
ILD, interstitial lung disease; qd, once-daily dosing

Ramalingam et al. ELCC 2016

EUROPEAN LUNG CANCER CONFERENCE 2016
## Summary of adverse events in osimertinib first-line cohorts

<table>
<thead>
<tr>
<th>AE category, all causality, n (%)</th>
<th>Safety analysis set*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 mg n=30</td>
</tr>
<tr>
<td>Any AE</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Any AE ≥Grade 3</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Any AE leading to death</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to dose interruption</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Any AE leading to dose reduction†</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>11 (37)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE category, drug-related‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

*Safety analysis set
†AE leading to dose reduction
‡AE category, drug-related
Tumor response to osimertinib in first-line cohorts (investigator assessed)

![Graph showing best percentage change from baseline in target lesion size (eneverol)](image)

<table>
<thead>
<tr>
<th></th>
<th>80 mg n=30</th>
<th>160 mg n=30</th>
<th>Total N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td>67% (95% CI 47, 83)</td>
<td>87% (95% CI 69, 96)</td>
<td>77% (95% CI 64, 87)</td>
</tr>
<tr>
<td>Disease control rate*</td>
<td>93% (95% CI 78, 99)</td>
<td>100% (95% CI 88, 100)</td>
<td>98% (95% CI 89, 100)</td>
</tr>
<tr>
<td>Best objective response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Partial response</td>
<td>20</td>
<td>24</td>
<td>44</td>
</tr>
<tr>
<td>Stable disease ≥6 weeks</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>


Ramalingam et al ELCC 2016

January 2016 RECIST 1.1, programatically calculated from investigator-recorded tumour measurement.

*Complete response, partial response, stable disease

CI, confidence interval; D, discontinuation; ORR, objective response rate
PFS in osimertinib first-line cohorts

Number of patients at risk:
- 80 mg: 30, 26, 23, 22, 20, 16, 14, 7, 0, 0
- 160 mg: 30, 29, 27, 23, 20, 19, 7, 0, 0, 0

Graph showing probability of PFS survival over months.

<table>
<thead>
<tr>
<th></th>
<th>80 mg n=30</th>
<th>160 mg n=30</th>
<th>Total N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS,* months (95% CI)</td>
<td>NC (12.3, NC)</td>
<td>19.3 (11.1, 19.3)</td>
<td>19.3 (13.7, NC)</td>
</tr>
<tr>
<td>Remaining alive and progression-free,† % (95% CI)</td>
<td>75 (55, 88)</td>
<td>69 (49, 83)</td>
<td>72 (59, 82)</td>
</tr>
<tr>
<td>12 months</td>
<td>57 (36, 73)</td>
<td>53 (32, 70)</td>
<td>55 (41, 67)</td>
</tr>
<tr>
<td>18 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ramalingam et al ELCC 2016
Clinical outcome in patients with de novo T790M positive NSCLC

A total of 5 (8%) patients had *de novo* T790M positive NSCLC at study entry (central testing)*

<table>
<thead>
<tr>
<th>Dose</th>
<th>Gender, M/F</th>
<th>Race</th>
<th>Age, years</th>
<th>Best objective response</th>
<th>DoR, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>F</td>
<td>Asian</td>
<td>50</td>
<td>Partial response</td>
<td>12.2</td>
</tr>
<tr>
<td>80 mg</td>
<td>F</td>
<td>Asian</td>
<td>60</td>
<td>Partial response</td>
<td>12.5</td>
</tr>
<tr>
<td>80 mg</td>
<td>F</td>
<td>Caucasian</td>
<td>61</td>
<td>Partial response</td>
<td>16.8</td>
</tr>
<tr>
<td>80 mg</td>
<td>F</td>
<td>Caucasian</td>
<td>49</td>
<td>Partial response</td>
<td>20.7</td>
</tr>
<tr>
<td>160 mg</td>
<td>M</td>
<td>Asian</td>
<td>59</td>
<td>Partial response</td>
<td>18.0</td>
</tr>
</tbody>
</table>

*1 patient with single *de novo* T790M mutation without co-existing sensitising mutation, 4 patients with T790M/L858R co-existing sensitising mutation
**FLAURA Study Design**

**Enrollment by local* or central#**

- **EGFR mutation testing of biopsy sample**

**Stratified by:**

- RECIST 1.1 assessment every 6 weeks until objective progressive disease
- Patients randomized to standard of care may receive AZD9291 after progression§

**Randomize patients 1:1**

**AZD9291 (80 mg p.o. qd)**

**EGFR-TKI standard of care##:**

- gefitinib (250 mg p.o. qd) or erlotinib (150 mg p.o. qd)

**RECIST 1.1 assessment every 6 weeks until objective progressive disease**

- Patients randomized to standard of care may receive AZD9291 after progression§

**Primary objective: efficacy by PFS**

---

*With central laboratory assessment performed for sensitivity

#cobas™ EGFR Mutation Test (Roche Molecular Systems)

##Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation

§Patients randomized to the standard of care treatment arm may receive open-label treatment with AZD9291 on central confirmation of both objective disease progression and T790M tumor

OS, overall survival; PFS2, second progression-free survival (time from randomization to second progression); p.o., orally
Phase II/III trial of Afatinib +/- Cetuximab in 1st line therapy of EGFR-mutated NSCLC (S1403)

Stage IIIB-IV NSCLC with EGFR mutation

1st Line
EGFR TKI naive

Afatinib*

Afatinib + Cetuximab*

*at PD: Biopsy for genomic study & PDX development (selected patients)

PD: Progressive Disease
PDX: patient-derived xenograft

PI: Sarah Goldberg
Co-PI: Rogerio Lilenbaum
Translational PI: Katerina Politi
ALK RESISTANCE
Mechanisms of acquired resistance to ALK inhibitor therapy

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example Mutations</th>
<th>Additional Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib resistance</td>
<td>I1171T/N/S, G1202R</td>
<td>cMET amplification, Ligand activation (EGFR or cMET activation)</td>
</tr>
<tr>
<td>Ceritinib resistance</td>
<td>F1174C/V, G1202R</td>
<td>MEK-activating mutation</td>
</tr>
</tbody>
</table>

EMT (MED12, cell line) BIM? Microenvironment? CNS penetration
# Next-generation ALK TKIs

<table>
<thead>
<tr>
<th>ALK TKI</th>
<th>Status</th>
<th>Ongoing Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceritinib</td>
<td>FDA Approved</td>
<td>Phase 3 v. chemo</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Approved in Japan &amp; US</td>
<td>Phase 3 v. crizotinib</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>Investigational, FDA Breakthrough</td>
<td>Phase 2</td>
</tr>
<tr>
<td>X-396</td>
<td>Investigational</td>
<td>Phase 1/2a</td>
</tr>
<tr>
<td>TSR-011</td>
<td>Investigational</td>
<td>Phase 1/2a</td>
</tr>
<tr>
<td>RXDX-101</td>
<td>Investigational</td>
<td>Phase 1/2a</td>
</tr>
<tr>
<td>PF-06463922</td>
<td>Investigational</td>
<td>Phase ½</td>
</tr>
<tr>
<td>CEP-37440</td>
<td>Investigational</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>
Response to Ceritinib, most post crizotinib

PFS with alectinib in crizotinib-resistant ALK+ NSCLC patients

Median PFS 8.9 months (95% CI 5.6–11.3)
58% of patients with event

Updated analysis cut-off 8 Jan 2015
Gadgeel SM Lancet Oncol 2014; Ou SH J Clin Oncol 2015 (abstract 8008)
S1400: MASTER LUNG-1
Squamous Lung Cancer

Matched Sub-studies
- **PI3K**
- **CDK4/6**
- **FGFR1**
- **HRD**

Non-match Sub-studies
- Checkpoint Naive
  - **GDC-0032**
  - **Palbociclib**
  - **AZD4547**
  - **BMN 673**
- Checkpoint Refractory
  - **Nivo/Ipi**
  - **MEDI4736/Treme**

Stage 1
- **GDC-0032** vs SoC
- **Palbociclib** vs SoC
- **AZD4547** vs SoC
- **BMN 673** vs SoC

Stage 2
- **GDC-0032** vs SoC
- **Palbociclib** vs SoC
- **AZD4547** vs SoC
- **BMN 673** vs SoC

- Lung-MAP amended to 2nd line therapy and beyond to accommodate Nivolumab approval
- Pre-screening added back
- Eligibility criteria broadened; *Sub-studies in development
LIQUID BIOPSY
TISSUE will always be the ISSUE

- Targeted therapies prolong survival\(^1\) YET 1/3 of non-squamous NSCLC patients are not tested for genetic targets
- In our DDU, 541 pts with solid tumors enrolled on phase I trials. 20% of screen fails (35 pts) will be unable to participate due to tissue QNS bx
- 2015 MDACC study evaluating the feasibility of genomic testing reported 600 pts (23%) ineligible due to tissue inadequacy\(^2\)
- Biopsy costs $14000; 20% have related complications\(^3\)

\(^1\)Kris JAMA 2014; \(^2\)Meric Bernstam JCO 2015 \(^3\)Lokhandwala Multidisciplinary Symposium in Thoracic Oncology Chicago Lung Meeting 2014
CTDNA TECHNOLOGIES HIGHLY SENSITIVE; LESS CUMBERSOME THAN CTC DETECTION

cTDA≠CTCs

Crowley et. al., Nature Reviews, 2013
Liquid Biopsies: “The Stethoscope For The Next 200 Years”

Mutations in tumor can also be found in the blood \(^2,^3\)

Plasma vs. Serum

---

\(^1\) Eric Topol, Professor of Genetics, The Wall Street Journal; \(^2\) Sorenson et al. Cancer Epidemiol Biomarkers Prev 1994; \(^3\) Diehl PNAS 2005;
POTENTIAL ADVANTAGES OF PLASMA-BASED TESTING

• Ease, rapid turn-around time
• Serial monitoring in “real time”
• Identify genomic alterations
• Determine emergence of molecular resistance
• “Summation” of tumor heterogeneity
## TECHNOLOGIES FOR DETECTION OF CT-DNA

<table>
<thead>
<tr>
<th>Principles of Detection</th>
<th>Method Ex.</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative PCR</td>
<td>Real-time PCR</td>
<td>Lowest cost, ease of use</td>
</tr>
<tr>
<td></td>
<td>ARMS/Scorpion PCR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mutant allele-specific PCR</td>
<td></td>
</tr>
<tr>
<td>Digital PCR</td>
<td>BEAMing</td>
<td>Highest sensitivity, limited genomic loci</td>
</tr>
<tr>
<td></td>
<td>Droplet digital PCR (ddPCR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microfluidic digital PCR</td>
<td></td>
</tr>
<tr>
<td>Next-Generation Sequencing</td>
<td>Hybrid capture based NGS</td>
<td>High sensitivity, broad range of genomic coverage</td>
</tr>
<tr>
<td></td>
<td>CAPP-Seq</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAm-Seq</td>
<td></td>
</tr>
</tbody>
</table>

Adapted, Qin et al., Chinese Journal of Cancer 2016
PLASMA-BASED TESTING—READY FOR PRIME TIME?
## COMPARISON OF METHODS OF CTDNA DETECTION

<table>
<thead>
<tr>
<th>Detection Method</th>
<th>Commercial Test</th>
<th>Analytical Sensitivity</th>
<th>Analytical Specificity</th>
<th>Cost</th>
<th>TOT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next-Generation Sequencing</td>
<td>Guardant 360</td>
<td>&gt;85%</td>
<td>99.99%</td>
<td>$5600</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Foundation ACT™</td>
<td>&gt;95%</td>
<td>99%</td>
<td>$5800</td>
<td>14</td>
</tr>
<tr>
<td>Digital PCR</td>
<td>Biodesix</td>
<td>&gt;85%</td>
<td>100%</td>
<td>$1800</td>
<td>3</td>
</tr>
<tr>
<td>Quantitative PCR+Sanger</td>
<td>Biocept</td>
<td>97%</td>
<td>99.5%</td>
<td>$1900</td>
<td>7</td>
</tr>
<tr>
<td>Quantitative PCR+NGS</td>
<td>Trovagene</td>
<td>93%</td>
<td>99%</td>
<td>$1800</td>
<td>14</td>
</tr>
</tbody>
</table>
POTENTIAL CLINICAL UTILITY OF PLASMA-BASED TESTING

- 54 yo M never-smoker with SOB
- s/p thoracentesis. Cytology= adenocarcinoma
- Molecular analysis (tissue): DNMT3A
- s/p 6 cycles Carbo/Pemetrexed/Avastin fb Pemetrexed/Avastin maintenance
- s/p 4 cycles Nivolumab
- Plasma-based testing was performed
- s/p 3 cycles Docetaxel/Ramucirumab
- Now feeling well s/p 8 months successful treatment on EGFR-TKI
Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer

Adrian G. Sacher, MD1,2; Cloud Paweletz, PhD3; Suzanne E. Dahlberg, PhD4,5; Ryan S. Alden, BSc1; Allison O'Connell, BSc3; Nora Feeney, BSc3; Stacy L. Mach, BA1; Pasi A. Jänne, MD, PhD1,2,3; Geoffrey R. Oxnard, MD1,2

[+] Author Affiliations

JAMA Oncol. Published online April 07, 2016. doi:10.1001/jamaoncol.2016.0173

This article was corrected | View correction
Plasma ddPCR – assay characteristics

<table>
<thead>
<tr>
<th>Assay</th>
<th>specificity</th>
<th>Positive Predictive Value</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR exon 19 del &amp; L858R</td>
<td>100%</td>
<td>100%</td>
<td>79%</td>
</tr>
<tr>
<td>EGFR exon 19 del</td>
<td>100%</td>
<td>100%</td>
<td>82%</td>
</tr>
<tr>
<td>EGFR L858R</td>
<td>100%</td>
<td>100%</td>
<td>74%</td>
</tr>
<tr>
<td>EGFR T790M</td>
<td>63%</td>
<td>79%</td>
<td>77%</td>
</tr>
<tr>
<td>KRAS G12X</td>
<td>100%</td>
<td>100%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Plasma ddPCR is highly specific and moderately sensitive with respect to the detection of EGFR and KRAS mutations in newly diagnosed patients. This assay exhibits a wide dynamic range which may be exploited for serial monitoring of mutation concentration in response to therapy. Median turnaround time of plasma ddPCR is 3 business days.

Abstract 935
Sacher and Oxnard JAMA Oncol 2016
Molecular Disease Monitoring

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

Sarah-Jane Dawson, F.R.A.C.P., Ph.D., Dana W.Y. Tsui, Ph.D.,
Muhammed Murtaza, M.B., B.S., Heather Biggs, M.A.,
Oscar M. Rueda, Ph.D., Suet-Feung Chin, Ph.D., Mark J. Dunning, Ph.D.,
Davina Gale, B.Sc., Tim Forshew, Ph.D., Betania Mahler-Araujo, M.D.,
Sabrina Rajan, M.D., Sean Humphray, B.Sc., Jennifer Becq, Ph.D.,
David Halsall, M.R.C.Path., Ph.D., Matthew Wallis, M.B., Ch.B.,
David Bentley, D.Phil., Carlos Caldas, M.D., F.Med.Sci.,
and Nitzan Rosenfeld, Ph.D.

Primary Outcome:
- Evaluate ctDNA assay sensitivity vs. CTCs, CA15-3
- N=50
- ddPCR assays: TP53, PI3KCA
- TAm-Seq, WGS also used

Dawson SJ et al NEJM 2013
MONITORING TREATMENT RESPONSES

- Changes in levels of circulating tumor DNA closely follow treatment responses
- Tracking levels of circulating tumor DNA may provide an early indicator of treatment resistance

Dawson SJ et al NEJM 2013
Analysis of EGFR T790M in tumor, urine and plasma

A. Urine vs Tissue

<table>
<thead>
<tr>
<th>T790M</th>
<th>FFPE Tumor, n</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Urine, n</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>13</td>
</tr>
</tbody>
</table>

B. Plasma vs Tissue

<table>
<thead>
<tr>
<th>T790M</th>
<th>FFPE Tumor, n</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Plasma, n</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Failed</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>13</td>
</tr>
</tbody>
</table>

C. Urine vs Plasma

<table>
<thead>
<tr>
<th>T790M</th>
<th>Plasma, n</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Urine, n</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>8</td>
</tr>
</tbody>
</table>

D. T790M-positive cases

- Tissue: 6 cases
- Urine: 1 case
- Plasma: 1 case
- Total: 8 cases

Positive by any one specimen type: 56 of 60 (93%)
Positive by tissue: 44 of 60 (73%)
Positive by plasma: 49 of 60 (82%)
Positive by urine: 45 of 60 (75%)
Positive by urine and plasma combined: 56 of 60 (93%)
Negative by any one specimen type: 4 of 60 (7%)
Dynamic monitoring of EGFR T790M during therapy with rociletinib

A

B

<table>
<thead>
<tr>
<th>Patient</th>
<th>% Change in Urine T790M at Day 21</th>
<th>% Tumor Shrinkage at Day 42</th>
<th>Best Overall Confirmed Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-94*</td>
<td>-38</td>
<td>PR</td>
</tr>
<tr>
<td>6</td>
<td>-94</td>
<td>-21</td>
<td>SD</td>
</tr>
<tr>
<td>7</td>
<td>-70</td>
<td>11</td>
<td>PD</td>
</tr>
<tr>
<td>9</td>
<td>-93</td>
<td>-33</td>
<td>SD</td>
</tr>
<tr>
<td>10</td>
<td>-97</td>
<td>-41</td>
<td>SD</td>
</tr>
<tr>
<td>12</td>
<td>-83</td>
<td>-52</td>
<td>SD</td>
</tr>
<tr>
<td>13</td>
<td>-51</td>
<td>20</td>
<td>PD</td>
</tr>
<tr>
<td>14</td>
<td>-86</td>
<td>-30</td>
<td>SD</td>
</tr>
<tr>
<td>15</td>
<td>-100</td>
<td>-42</td>
<td>PR</td>
</tr>
</tbody>
</table>

READY FOR PRIME TIME?—NOT YET

• This is not a CBC
• Analytical vs. Clinical validity
• More work needed to determine clonal vs. branch mutations
• Assay comparisons limited and problematic
FDA approves first blood test to detect gene mutation associated with non-small cell lung cancer

For Immediate Release

June 1, 2016

The U.S. Food and Drug Administration today approved the cobas EGFR Mutation Test v2, a blood-based companion diagnostic for the cancer drug Tarceva (erlotinib). This is the first FDA-approved, blood-based genetic test that can detect epidermal growth factor receptor (EGFR) gene mutations in non-small cell lung cancer patients. Such mutations are present in approximately 10-20 percent of non-small cell lung
SUMMARY

- Rapid, less-invasive molecular profiling is attractive, but doesn’t obviate the need for tissue
- Clinical validation should be the goal of needed prospective clinical trials
- ctDNA may be the “stethoscope of the next 200 years,” but don’t take away my CT scan just yet
Patients respond to multiple therapies and sequencing can improve outcomes

1st gen
8-13 mo

3rd gen
8-10 mo

Chemo
4+

Immunotherapy
3+?

3rd gen 19 mo

1st gen
unknown

Chemo
4+

Immunotherapy
3+?

1st gen/bev or combination
16 mo

3rd gen
7-13 mo

Immunotherapy
3++?

Chemo
4+
With tumor heterogeneity in NSCLC, options for targeted therapy and overcoming resistance may become more personalized.

Patterns of resistance will help to guide subsequent therapy, and choice of first-line therapy.

Liquid biopsies will allow for sequencing after progression.

Improved survival with maintained quality of life is the ultimate goal and sequencing will be important.

New targets and agents are under investigation and show promise: NTRK, MET, RET...
Questions?

THANK YOU