Beyond ALK and EGFR: Novel Molecularly Driven Targeted Therapies in NSCLC

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DISCLOSURE OF INTEREST

Personal financial interests
- None

Institutional financial interests
- Expert Meeting/Advisory Board sponsored by BMS, Takeda, AbbVie, Boehringer-Ingelheim.

Non-financial interests
- Principal Investigator for SCAN-LEAF, an epidemiological study sponsored by BMS.
Molecular Subtyping of Non-Small Cell Lung Cancer

Non-small cell lung cancer as one disease

Subtyping based on histology

Adenocarcinoma

- EGFR-sensitising (15%)
- EGFR other (2%)
- KRAS (25%)
- ALK (7%)
- HER2 (2%)
- BRAFV600E (2%)
- BRAF other (1%)
- ROS1 (2%)
- RET (2%)
- NTRK1 (0.5%)
- MET (3%)
- MAP3K1 (0.5%)
- PIK3CA (1%)
- NRAS (0.5%)
- >1 mutation (3%)
- Unknown (31%)

Squamous Cell Carcinoma

- EGFR (8%)
- DDR2 (4%)
- FGFR1 (17%)
- PIK3CA (14%)
- PTEN (18%)
- PDGFRα (9%)
- FGFR2 (3%)
- Unknown

Adenocarcinoma

- Squamous cell carcinoma 34%
- Other 11%
- Adenocarcinoma 55%
Targets Beyond EGFR och ALK?

- **ROS1** - crizotinib EMA approved (August 2016)
- **BRAF** – dabrafenib+trametinib EMA approved (April 2017)
- **RET**
- **MET**
- **HER2**
- **NTRK1**
- **FGFR1**
- **PIK3CA**
- **DDR2**

and more
Rearrangements of ROS1 in NSCLC

- Belongs to the sevenless sub-family of insulin-receptor genes
- Orphan receptor
- Expressed during development, physiological function unknown
- In 1-2% of NSCLC
- More frequent in patients who are younger, never/light smokers, adenocarcinoma
- No overlap with other oncogene drivers
ROS1 Targeting Agents in NSCLC

(A) Crizotinib
(B) Lorlatinib
(C) Ceritinib
(D) Entrectinib
(E) Cabozantinib
Tumor responses with Crizotinib in \textit{ROS1}-rearranged NSCLC: Updated Results from PROFILE 1001

**Best Percent Change From Baseline in Size of Target Lesions (n=51)\textsuperscript{a,b}**

- ORR 69.8 \%
- CR \(n=5\)
- PR \(n=32\)
- SD \(n=11\)

**mPFS 19.3 m**

\textsuperscript{a}Tumor assessment by RECIST v1.1.
\textsuperscript{b}Excludes 2 patients: one with early death and one with indeterminate response.
\textsuperscript{c}Data as of cutoff date of 30 November 2014.

32 patients:

**ORR** 62%

**DCR** 81%

(CR 3%, PR 59%, SD 19%)

Phase 2 Study of Lorlatinib in Patients With Advanced ALK+/ROS1+ Non-Small Cell Lung Cancer

Benjamin J. Solomon,1 Alice T. Shaw,2 Sai-Hong I. Ou,3 Benjamin Besse,4 Enriqueta Felip,5 Todd M. Bauer,6 Ross A. Soo,7 Alessandra Bearz,8 Chia-Chi Lin,9 Jill S. Clancy,10 Antonello Abbattista,11 Holger Thurm,12 Gerson Peltz,13 Elizabeth T. Masters,14 Jean-François Martini,12 Leonard P. James,14 Takashi Seto15

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**Efficacy in EXP6 (ROS1+ With Any Prior Treatment)**

**EXP6**  
(n=47)

| ORR, n/N (%) | 17/47 (36) | (95% CI) | (23, 52) |
| IC ORR, n/N (%) | 14/25 (56) | (95% CI) | (35, 76) |

**Median DOR, mo**  
(95% CI)  
13.8  
(11.1, NR)

**DOR ≥6 mo, n⁰/n (%)**  
12/17 (71)

**Median PFS, mo**  
(95% CI)  
9.6  
(4.7, NR)

- 25 patients (53%) had brain metastases at baseline.

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**Overall**

- Complete response
- Partial response
- Stable disease
- Progressive disease (PD)
- Indeterminate

**Intracranial**

- Off treatment or PD occurred

# Previously received crizotinib

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CI, confidence interval; DOR, duration of response; mo, months; NR, not reached.

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*a, b Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

*b Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of –100% are shown as partial responses due to the inclusion of non-target lesions in the summary.
Crizotinib Treatment Resistance in ROS1

A

![Diagram showing structures of ROS1 and ALK with mutations highlighted]

B

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<tr>
<th></th>
<th>Gatekeeper L2026M</th>
<th>αC helix S1986Y/F</th>
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<th>Solvent front D2033N</th>
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Lin and Shaw, Journal of Thoracic Oncology 2017 12, 1611-1625
**ROS1-rearranged NSCLC**

- Crizotinib
  - Oligoprogression
    - Consider local ablative therapy with continued crizotinib

Repeat tumor (or liquid) biopsy at the time of progression (if feasible and safe)

**ROS1 resistance mutation**

- Non-G2032R mutation
  - Next-generation ROS1 TKIs (e.g., lorlatinib, TPX-0005, DS-6051b)

- G2032R mutation
  - ROS1 TKIs with preclinical G2032R activity (e.g., TPX-0005)
    - Cabozantinib (off-label)
    - Chemotherapy

**No ROS1 resistance mutation**

- CNS-only progression
  - ROS1 TKIs with superior CNS penetration [e.g., ceritinib (off-label), entrectinib, or lorlatinib]

- Systemic progression
  - Combination strategies
    - Chemotherapy
  - Next-generation ROS1 TKIs
RAS/Raf/MEK/Erk signalling pathway in NSCLC

BRAF mutations in kinase domain

V600E ~ 55%
G469A ~35%
D594G ~10%
Braf Inhibition in NSCLC: Single Agent Activity

**Vemurafenib**
N=20
90% BRAF V600E
ORR: 42%
mPFS: 7.3 mo
mOS NR

**Dabrafenib**
N=78
100% BRAF V600E
ORR: 33%, mPFS: 5.5 mo
mOS: 12.7 mo

**EURAF Study BRAFi**
ORR 53%, DCR 85%, mPFS 5.0 mo, mOS 10.8 mo
Dabrafenib/trametinib in previously treated BRAF V600E patients

ORR 63%
DCR 75.4%
mPFS 8.6 mo
(independent assessment, n=57)


Dabrafenib/trametinib in previously untreated BRAF V600E patients

ORR 64%
DCR 72%
mPFS 14.6 mo
(independent review, n=36)

RET – Rearranged during Transfection – in 1-2% of NSCLC

RET fusions reported in the literature are depicted including major recurrent KIF5B–RET fusions, CCDC6–RET, NCOA4–RET (14–16, 20), and the novel TRIM33–RET.


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Overall response rates of multikinase inhibitors in patients with rearranged during transfection proto-oncogene gene (RET)-rearranged NSCLC, by study. *, Phase I; °, phase II, and ϕ, retrospective.

LURET STUDY: PHASE 2 STUDY OF VANDETANIB IN PTS WITH ADVANCED RET-REARRANGED NSCLC

Figure 2. Study profile

- Screening for RET fusions
  n = 1536
- RET-positive patients
  n = 34 (2%)
- Enrolled patients
  n = 19 (ITT population)
  2 patients were found to be ineligible for potassium criterion after enrollment.
- Eligible patients
  n = 17 (Primary analysis population)
(The data-cutoff date was August 31, 2015)

Table 2. Efficacy according to the type of RET fusion

<table>
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<tr>
<th>Outcome</th>
<th>All (N = 19)</th>
<th>KIF5B-RET (N = 10)</th>
<th>CCDC6-RET (N = 6)</th>
<th>Unknown (N = 3)</th>
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<tbody>
<tr>
<td>ORR, %</td>
<td>47 (24, 71)</td>
<td>20 (3, 56)</td>
<td>83 (36, 99.6)</td>
<td>67 (9, 99)</td>
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<tr>
<td>(95% CI)</td>
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<td>DCR, %</td>
<td>90 (67, 99)</td>
<td>90 (56, 99.7)</td>
<td>100 (54, 100)</td>
<td>67 (9, 99)</td>
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<tr>
<td>(95% CI)</td>
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<tr>
<td>Median PFS, mo</td>
<td>4.7 (2.8, 8.5)</td>
<td>2.9 (1.1, 15.7)</td>
<td>8.3 (4.7, 8.5)</td>
<td>4.7 (1.0, 10.9)</td>
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<tr>
<td>(95% CI)</td>
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<td>1-yr OS, %</td>
<td>47 (21, 69)</td>
<td>42 (11, 71)</td>
<td>67 (5, 95)</td>
<td>33 (1, 77)</td>
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<tr>
<td>(95% CI)</td>
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Global RET registry

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<th>RET Inhibitor</th>
<th>Best response (%; 95% CI)</th>
<th>Median PFS (95% CI)</th>
<th>Median OS (95% CI)</th>
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<tr>
<td>Cabozantinib (21)</td>
<td>37% (95% CI : 16.3; 61.6)</td>
<td>3.6 months (1.3-7.0 months)</td>
<td>4.9 months (1.9-14.3 months)</td>
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<td>Vandetanib (11)</td>
<td>18% (95% CI : 2.3; 51.8)</td>
<td>2.9 months (1.0-6.4 months)</td>
<td>10.2 months (2.4-NR months)</td>
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<tr>
<td>Sunitinib (10)</td>
<td>22% (95% CI : 2.8; 60.0)</td>
<td>2.2 months (0.7-5.0 months)</td>
<td>6.8 months (1.1-NR months)</td>
</tr>
</tbody>
</table>

Largest database (n=165 pts, 53 pts treated with RET inhibitors)
TARGETING RET

• Several RET inhibitor compounds, initially designed to target other tyrosine kinases

• At present phase II vandetanib, cabozantinib, lenvatinib, with moderate activity and substantial toxicity (activity against VEGFR kinases)

• New studies with RET inhibitors:


  - ETOP trial: alectinib for RET-rearranged NSCLC (ALERT lung trial)
- **History of MET spans > 3 decades**
  - MET proto-oncogene first discovered in the mid-1980s
  - MET found to be dysregulated in lung cancers in the mid-1990s

- **More than 20 targeted therapies targeting MET or its ligand have been developed.**

- **No targeted therapy approved to date for patients with cancers driven by MET.**
MET in resistance to EGFR TKIs

acquired resistance to 1st generation EGFR TKI therapy in EGFR-mutant lung cancers

acquired resistance to 3rd generation EGFR TKI therapy in EGFR-mutant lung cancers

MET amplification also found in TKI-naïve metastatic EGFR-mutant lung cancers

MET mutation no concurrence with known driver mutations but tended to coexist with MET amplification or copy number gain (P < 0.001) (Awad et al. J Clin Oncol. 2016 Mar 1;34(7):721-30)

- Incidence
  - 3-4% of nonsquamous NSCLCs
  - 8-30% of sarcomatoid lung carcinomas

- Clinicopathologic features
  - older patients
  - ↓ proportion of never smokers
  - mutually exclusive with other drivers
  - 15-20% with concurrent MET amplification
## Randomized Trials with Anti-MET Agents in Lung Cancer

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<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Population</th>
<th>MET abnormalities</th>
<th>Setting</th>
<th>Arms</th>
<th>N</th>
<th>Primary endpoint</th>
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<td>OS</td>
<td>5.9</td>
<td>(p = 0.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>MET GCN ≥ 4</td>
<td>Pretreated</td>
<td>Erlotinib + Placebo</td>
<td>154</td>
<td>OS</td>
<td>12.7</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>MET GCN ≥ 4</td>
<td>Pretreated</td>
<td>Erlotinib + Placebo</td>
<td>153</td>
<td>OS</td>
<td>11.1</td>
<td>(p = 0.427)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>MET GCN ≥ 4</td>
<td>Pretreated</td>
<td>Erlotinib + Placebo</td>
<td>83</td>
<td>OS</td>
<td>8.3</td>
<td>(n.r.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>MET GCN ≥ 4</td>
<td>Pretreated</td>
<td>Erlotinib + Placebo</td>
<td>77</td>
<td>OS</td>
<td>7.7</td>
<td>(n.r.)</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>E1512 [42]</td>
<td>Non-squamous</td>
<td>Unselected</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Erlotinib + Cabozantinib</td>
<td>43</td>
<td>PFS</td>
<td>4.7</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>Wt-EGFR</td>
<td>IHC MET-positive (2+ or 3+ in ≥50% of TC)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Cabozantinib arms</td>
<td>40</td>
<td>PFS</td>
<td>4.3</td>
<td>(p = 0.003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wt-EGFR</td>
<td>IHC MET-positive (2+ or 3+ in ≥50% of TC)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Erlotinib</td>
<td>42</td>
<td>PFS</td>
<td>1.8</td>
<td>0.39#</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC SD after 12 weeks of cabozantinib</td>
<td>Unselected</td>
<td>Pretreated</td>
<td>Erlotinib</td>
<td>50</td>
<td>PFS</td>
<td>5.0</td>
<td>(p = 0.003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wt-EGFR</td>
<td>IHC MET-positive (1+ or 2+ or 3+)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Cabozantinib arms</td>
<td>24</td>
<td>PFS</td>
<td>1.8</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>IHC MET-positive (2+ or 3+ in ≥10% of TC)</td>
<td>Pretreated</td>
<td>Cabozantinib arms</td>
<td>8</td>
<td>PFS</td>
<td>2.3</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>IHC MET-positive (2+ or 3+ in ≥60% of TC)</td>
<td>Pretreated</td>
<td>Placebo</td>
<td>7</td>
<td>PFS</td>
<td>2.4</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td>NCT00940225 [117]</td>
<td>NSCLC EGFR mutant</td>
<td>IHC MET-positive (2+ or 3+ in ≥10% of TC)</td>
<td>Pretreated</td>
<td>Emibetuzumab</td>
<td>28</td>
<td>ORR</td>
<td>4.3%</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td>Phase II RDT</td>
<td>NSCLC EGFR mutant</td>
<td>IHC MET-positive (2+ or 3+ in ≥10% of TC)</td>
<td>Pretreated</td>
<td>Emibetuzumab</td>
<td>83</td>
<td>ORR</td>
<td>3.0%</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>IHC MET-positive (2+ or 3+ in ≥10% of TC)</td>
<td>Pretreated</td>
<td>Emibetuzumab</td>
<td>21</td>
<td>ORR</td>
<td>4.8%</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC</td>
<td>IHC MET-positive (2+ or 3+ in ≥10% of TC)</td>
<td>Pretreated</td>
<td>Emibetuzumab</td>
<td>53</td>
<td>ORR</td>
<td>3.8%</td>
<td>(n.r.)</td>
</tr>
</tbody>
</table>
Targeting \textit{MET} amplification

<table>
<thead>
<tr>
<th>MET Amplification Level</th>
<th>Low MET Amp, n=2</th>
<th>Intermediate MET Amp, n=6</th>
<th>High MET Amp, n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>0% (95%CI 0-84)</td>
<td>17% (95%CI 0-64)</td>
<td>67% (95%CI 22-96)</td>
</tr>
<tr>
<td>Median DoR</td>
<td>N/A</td>
<td>16 weeks</td>
<td>73.6 weeks</td>
</tr>
</tbody>
</table>

Multicenter phase 1 expansion cohort, **crizotinib** 250 mg twice daily

**Primary endpoint:** overall response

Camidge DR et al, ASCO 2014

- **Moro-Sibilot, WCLC 15:** 25 MET-amplified pts treated with **crizotinib** - PR 32\%, mPFS 3.2 m
- **Noonan, JTO 16:** The most appropriate method for defining MET amplification - uncertain FISH MET/CEP7 ratio of 5 or higher?
Response to Crizotinib in MET Exon 14-Altered Lung Cancers

Best Percent Change From Baseline in Size of Target Lesions (n=22)*

Objective response rate (ORR) 11/28 (39%, 95% CI: 22, 59)

Best overall response n (%)
- Complete response 2 (7)
- Partial response 9 (32)
- Stable disease 10 (36)
- Progressive disease 2 (7)
- Indeterminate 5 (18)

Median duration of response: 9.1 months (95% CI: 5.9, 10.5)

*Includes patients with measurable disease at baseline and ≥1 response assessment scan; excludes 1 patient with early death, 4 patients with indeterminate response and 1 patient (CR responder) with no measurable target lesions at baseline
OA 09.03: TATTON Ph Ib Expansion Cohort: Osimertinib plus Savolitinib for Pts with EGFR-Mutant MET-Amplified NSCLC after Progression on Prior EGFR-TKI – Ahn M-J, et al

• Key results
  – AEs of any grade and causality occurred in 92% of patients, with nausea (44%) and vomiting (35%) the most common
  – Grade ≥3 AEs were reported in 50% of patients
  – Preliminary anti-tumour activity was promising across all groups among patients with centrally confirmed MET-positive status

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Prior 3rd gen T790M-directed EGFR-TKI (n=25)</th>
<th>No prior 3rd gen T790M-directed EGFR-TKI</th>
<th>Total (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7 (28)</td>
<td>4 (57)</td>
<td>19 (40)</td>
</tr>
<tr>
<td>SD ≥6 weeks</td>
<td>13 (52)</td>
<td>3 (43)</td>
<td>22 (47)</td>
</tr>
</tbody>
</table>

• Conclusions
  – This phase 1b expansion cohort showed a safety profile consistent with the first phase of this study
  – Osimertinib + savolitinib showed anti-tumour activity in all the MET-positive groups, regardless of EGFR T790M mutation status or prior T790M-directed EGFR-TKI therapy

Targeting HER2 in Lung Cancer

- HER2 mutations 2% of lung cancer
- Most common exon 20 insertion (12 bp → YVMA)
- HER2 amplification
  ~ 3% of lung cancer EGFR TKI naive
  ~ 10% EGFR TKI resistance
Lung cancer patients with *HER2* mutations treated with chemotherapy and *HER2*-targeted drugs: results from the European EUHER2 cohort (101 patients)

Overall response rate (ORR), disease control (DC), progression-free survival (PFS, weeks), and overall survival (OS, weeks) according to drug type

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>ORR</th>
<th>DC</th>
<th>PFS median (95% CI)</th>
<th>OS median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line: without HER2-targeting treatment</td>
<td>93</td>
<td>43.5%</td>
<td>70.7%</td>
<td>6 (5; 7.1)</td>
<td>24 (19.1; 36.4)</td>
</tr>
<tr>
<td>Second-line: without HER2-targeting treatment</td>
<td>52</td>
<td>10%</td>
<td>36%</td>
<td>4.3 (3.1; 5)</td>
<td>19.4 (9.6; 24.7)</td>
</tr>
<tr>
<td>EGFR-TKI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26</td>
<td>7.6%</td>
<td>26.8%</td>
<td>2.99 (1.87; 4.47)</td>
<td>20.14 (7.14; 32.95)</td>
</tr>
<tr>
<td>Trastuzumab combination, T-DM1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58</td>
<td>50.9%</td>
<td>75.5%</td>
<td>4.8 (3.4; 6.5)</td>
<td>13.3 (8.1; 15)</td>
</tr>
<tr>
<td>Neratinib, lapatinib, and afatinib&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29</td>
<td>7.4%</td>
<td>55.5%</td>
<td>3.4 (2.4; 4)</td>
<td>6.5 (4.7; 30.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> If the same drug has been given more than one time, the results presented here are from their first administration.
T-DM1 in lung ADC with HER22 mutations

**Overall response rate (ORR) by RECIST v1.1**

**HER2 Mutant Lung Cancer Responses**

- Confirmed partial response
- Stable/progressive disease

**Patients**

% Best Response per RECIST v1.1

ORR 44% (8/18, 95% CI 22-69%), study met primary endpoint

**Progression free survival (PFS)**

- Median PFS: 4 months (95% CI 3.0 to NR, n=18 with 13 events)
- Median duration of response: 5 months (95% CI 3.0 to NR, n=8 with 6 events)

Li et al. J Clin Oncol 35, 2017 (suppl; abstr 8510)
T-DM1 in HER2 overexpressing lung ADC

Patient Disposition

<table>
<thead>
<tr>
<th>IHC 2+</th>
<th>IHC 3+</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients screened, n/N (%)</td>
<td>102/393 (26)</td>
<td>31/393 (8)</td>
</tr>
<tr>
<td>Patients enrolled, n</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>On treatment at clinical cutoff date, n</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Discontinuation of treatment, n</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Median follow-up, months (range)</td>
<td>18.0 (0.9-22.4)</td>
<td>14.3 (1.0-18.7)</td>
</tr>
</tbody>
</table>

First Patient In: December 15, 2014
Last Patient In: June 21, 2016
Clinical Cutoff: October 26, 2016

Treatment Response

- Median duration of response: 7.3 months (95% CI 2.9–8.3 months)

Change in Diameter from Baseline, %

IHC 2+

ORR=0% (95% CI 0.0, 11.9)

IHC 3+

ORR=20% (95% CI 5.7, 43.7)

*Indicates positive HER2 amplification; U indicates unknown HER2 amplification; All other patients’ ISH status is negative

*One patient is not displayed due to erroneous tumor measurements recorded for cycle 7; this patient was determined to have a best response of SD (screening tumor size 94 mm, C7D1 tumor size 70 mm).

NE: not evaluable/missing; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Treatment response as assessed by investigator.
HER2 in NSCLC – Other Studies

• HER2-mut and response to trastuzumab (Cappuzzo NEJM 06)

• Dacomitinib (Kris Ann Oncol 15)
  o 26 p with HER2-mut, 3 PR (12%) / mOS 9 mo
  o 4 p with HER2 amplification, no responses

• Stage I of a 2-stage phase II comparing neratinib with/without temsirolimus in NSCLC pts with HER2-mut (Besse ESMO 14)
  o 13 pts received neratinib, 14 pts neratinib/temsirolimus
  o Neratinib arm: 54% SD / 46% PD; PFS 2.9 mo
  o Neratinib/temsirolimus: 21% PR / 79% SD; PFS 4.0 mo

• Phase II study of T-DM1 monotherapy in relapsed NSCLC with documented HER2 positivity (Hotta JTO 2018)
  (IHC 3+, IHC 2+ and FISH+ or exon 20 mut)
  o 15 patients
  o PR 6.7% (1/15), SD 46.7%, PD 46.7%
  o mPFS 2.0 mo, mOS 10.9 mo

• Future aspects: 3rd gen EGFR TKI Osimertinib for HER2 aberrations (mouse models) (Liu CCR 2018), neratinib/trastuzumab in HER2 mutant lung cancer (patient derived tumor organoids) (Paweletz WCLC 2017)
**NTRK1** fusions in cancer

- **NTRK1** fusion originally identified in 1982\(^1,2\)
- **NTRK1** fusions first identified in NSCLC in 2013\(^3\)
- **MPRIP-NTRK1** and **CD74-NTRK1**
- NTRK fusions <1% in NSCLC
- Oncogene fusions also involve **NTRK2** and **NTRK3** with multiple gene partners\(^4\)

### Table: Gene fusions, Cancer, Frequency

<table>
<thead>
<tr>
<th>Gene fusion</th>
<th>Cancer</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK1</td>
<td>Lung adenocarcinoma</td>
<td>3/91 (3.3%)</td>
</tr>
<tr>
<td>NTRK1</td>
<td>Intrahepatic cholangiocarcinoma</td>
<td>1/28 (3.6%)</td>
</tr>
<tr>
<td>NTRK1</td>
<td>Colorectal cancer</td>
<td>3 isolated reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/96 (1.5%)</td>
</tr>
<tr>
<td>NTRK1</td>
<td>Papillary thyroid cancer</td>
<td>26/220 (12.3%)</td>
</tr>
<tr>
<td>NTRK1</td>
<td>Spitzoid neoplasms</td>
<td>23/140 (16.4%)</td>
</tr>
<tr>
<td>NTRK1</td>
<td>Glioblastoma</td>
<td>2/185 (1.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/162 (2.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/157</td>
</tr>
<tr>
<td>NTRK1</td>
<td>Sarcoma (TCGA)</td>
<td>1/103 (1%)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>Astrocytoma</td>
<td>3/96 (3.1%)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>Lung adenocarcinoma (TCGA)</td>
<td>1/513 (0.2%)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>Head and neck squamous cell carcinoma (TCGA)</td>
<td>1/411 (0.2%)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>Brain lower grade glioma (TCGA)</td>
<td>2/461 (0.4%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Secretory breast carcinoma</td>
<td>12/13 (92%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Mammary analogue secretory carcinoma</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Papillary thyroid cancer</td>
<td>9/62 (14.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/243 (2.9%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Acute myeloid leukemia</td>
<td>2 case reports</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Congenital mesoblastic nephroblastoma</td>
<td>5/9 (55%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Congenital fibrosarcoma</td>
<td>5/11 (45.5%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Ph-like acute lymphoblastic leukemia</td>
<td>1/154 (0.7%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Colon adenocarcinoma (TCGA)</td>
<td>2/286 (0.7%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Thyroid carcinoma (TCGA)</td>
<td>7/498 (1.5%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Skin cutaneous melanoma (TCGA)</td>
<td>1/374 (0.3%)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Head and neck squamous cell carcinoma (TCGA)</td>
<td>1/411 (0.2%)</td>
</tr>
</tbody>
</table>

\(^1\)Pulciani Nature 18982; \(^2\)Martin-Zanca et al., Nature 1986
\(^3\)Vaishnavi et al., Nat Med 2013; \(^4\)Vaishnavi et al., Cancer Discov 2015
Multi-Targeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib (RXDX-101): Combined Results from Two Phase 1 Trials (ALKA-372-001 and STARTRK-1)

Baseline and on-study brain MRI images for a patient with SQSTM1-NTRK1-rearranged lung cancer

n= 24

NSCLC

Efficacy of larotrectinib in NTRK1/2/3 fusion cancers

ORR = 76% (n = 50)

Hyman et al., ASCO 2017
**Novel Targeted Therapies in Squamous Cell Carcinoma of the Lung**

63% of tumors can potentially be treated with targeted therapy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1 amplification</td>
<td>22% (15% CTGA)</td>
<td>FGFR TKIs</td>
</tr>
<tr>
<td>EGFRvIII mutation</td>
<td>5%</td>
<td>EGFR TKIs</td>
</tr>
<tr>
<td>PI3KCA mutation</td>
<td>3.6%</td>
<td>PI3KCA inhib.</td>
</tr>
<tr>
<td>EGFR TK mutation</td>
<td>3.4%</td>
<td>EGFR TKIs</td>
</tr>
<tr>
<td>DDR2 mutation</td>
<td>3.2%</td>
<td>Dasatanib</td>
</tr>
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</table>

Okashi and Pao, *Cancer Discovery*, April 2011
Clinical studies of FGFR-TKI

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Target</th>
<th>Clinical development (indication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivanib</td>
<td>Bristol-Myers Squibb</td>
<td>FGFR, VEGFR</td>
<td>Phase III (CRC, HCC, liver)</td>
</tr>
<tr>
<td>Dovitinib</td>
<td>Novartis</td>
<td>FGFR, PDGF, VEGFR, FLT3, c-KIT</td>
<td>Phase III (RCC)</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Eisai</td>
<td>FGFR, PDGF, VEGFR</td>
<td>Phase III (melanoma, thyroid)</td>
</tr>
<tr>
<td>Masitinib</td>
<td>AB Science</td>
<td>FGFR, PDGF, c-KIT</td>
<td>Phase III (GIST, melanoma, MM, pancreatic)</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>Boehringer Ingelheim</td>
<td>FGFR, PDGF, VEGFR</td>
<td>Phase III (NSCLC, ovarian)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>GlaxoSmithKline</td>
<td>FGFR1, FGFR2, VEGFR</td>
<td>Phase III (breast, lung, ovarian, RCC, STS)</td>
</tr>
<tr>
<td>PI-88</td>
<td>Progen</td>
<td>FGF1, FGF2, VEGF</td>
<td>Phase III (HCC, liver)</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Bayer</td>
<td>FGFR, PDGF, VEGFR, c-KIT, RET</td>
<td>Phase III (GIST, CRC)</td>
</tr>
<tr>
<td>TSU 68</td>
<td>Pfizer</td>
<td>FGFR, KDR, PDGF, VEGFR2</td>
<td>Phase III (HCC)</td>
</tr>
<tr>
<td>ENMD-2076</td>
<td>Entremed</td>
<td>FGFR1, KDR, FGFR2, PDGF, VEGFR, FLT3, c-KIT, Aurora K, FLT3</td>
<td>Phase II (ovarian)</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Ariad</td>
<td>FGFR, PDGF, VEGFR</td>
<td>Phase II (AML, CML)</td>
</tr>
<tr>
<td>E3810</td>
<td>Eisai</td>
<td>FGFR1, VEGFR</td>
<td>Phase I (solid tumors)</td>
</tr>
<tr>
<td>PBI-05204</td>
<td>Phoenix Bio</td>
<td>FGFR1, VEGFR, VEGFR</td>
<td>Phase I (solid tumors)</td>
</tr>
</tbody>
</table>

Small-molecule tyrosine kinase inhibitors: FGFR selective

| AZD4547           | AstraZeneca            | FGFR1-3                          | Phase II (breast, gastric)        |
| BGJ398            | Novartis               | FGFR1-3                          | Phase I (solid tumors)            |
| LY2874455         | Eli Lilly              | FGFR1-4                          | Phase I (solid tumors)            |

FGFR antibodies

| RG7444           | Roche                  | FGFR3                            | Phase I (MM)                      |

FGF-ligand traps

| FP-1039           | Five Prime Therapeutics | FGFR1, FGFR2, FGFR4 | Phase II (endometrial) |
Insulin-like Growth Factor Receptor-1 (IGF-1R) – still a dead end?

Crudden Front. Endocrinol., 27 April 2015

Patient with squamous cell carcinoma treated with PPP – an IGF-1R targeting agent

Figure 3. PET scan images from the three index lesions at baseline (upper panel) and the 12 week assessments (lower panel).

Index lesion 1

SUV max = 7.7 g/mL
Volume = 36.1 cm³

Index lesion 2

SUV max = 4.1 g/mL
Volume = 1.7 cm³

Index lesion 3

SUV max = 4.2 g/mL
Volume = 4.0 cm³

SUV max = 5.8 g/mL
Volume = 7.9 cm³

Total metabolic regress

Total metabolic regress

Challenges!
Tumour Heterogeneity

Burrell, Mcgranahan, Bartek and Swanton Nature 2013
More challenges

- Comprehensive molecular profiling
- Low frequency of many molecular aberrations
- Drug resistance
- How to combine different treatments (optimize effect, minimize toxicity)?
- Need of new predictive biomarkers for response and resistance
Design of clinical studies

Umbrella Trials

Single Type of Cancer: Test multiple drug-biomarker combinations

- BATTLE
- I-SPY2
- SWOG Lung MAP (S1400): adv SCCA
- ALCHEMIST: early stage NSCLC
- ALK Master Protocol: ALK+ NSCLC

Basket Trials

Multiple Cancer Types: Test multiple drugs against single or multiple biomarkers

- Imatinib Basket
- BRAF+
- NCI MATCH
  - TAPUR
  - DRUP
Biomarkers!

Clinical studies!

Gene expression (array, RT-PCR, nanostring)

Tumor genetic profiling (mutations, copy number, epigenetics)

Protein expression/modifications

Tumor

Clinical data

Blood-based markers (ctDNA, CTCs, exosomes)

Genetic profiling (SNPs, germ line)

Patient

Precision Cancer Medicine
Thank you for your attention!