GOING BEYOND EGFR

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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 and Merck Serono; for which I received honoraria.

I declare no conflict of interest.
Landmark NSCLC genetic maps

Ding, Nature 2008; Kris, ASCO 2011
Adenocarcinoma driver mutations: 1990
Adenocarcinoma driver mutations 2004-2008

Diagram showing the distribution of driver mutations with the majority being unknown.
2012 update on adenocarcinoma driver mutations
2012 update on adenocarcinoma driver mutations
Where to add tumour suppressors?

- KRAS
- EGFR
- LKB1
- PIK3CA
- MET
- PTEN
- HER2
- BRAF
- MEK1
- NRAS
- Unknown

Diagram showing the distribution of driver mutations.
2012 update on adenocarcinoma driver quantitative alterations
2012 update on driver rearrangements
The complex picture

Graphical representation of 45 fusion genes from 87 adenocarcinomas

Seo, Genome Res 2012
2012 update on squamous carcinoma driver mutations/ quantitative alterations

Squamous is even more complex – grouping by pathways?

HER2 mutation (HER2YVMA):
Drives rapid development of adenosquamous lung tumors in mice

**Definition of drivers?**

Perera, PNAS 2009
Development of lung adenocarcinoma in *EML4-ALK* transgenic mice:
Hundreds of adenocarcinoma nodules (arrows)

Soda, PNAS 2008
Drivers prevalence variability?

Frequency of Driver Mutations in Lung Adenocarcinoma from Female Never-Smokers ...

Zhang, CCR 2011
Drivers prevalence variability (2)?

Frequency of Driver Mutations in Lung Adenocarcinoma from Female Never-Smokers ... *varies with age, and histologic subtype*
Conclusion 1

Most patients with lung cancer will be stratified according to one (or more) oncogenic driver in the future. Potential therapeutic targets are also identified in squamous carcinoma – with a marked genomic complexity.

NEVERTHELESS:

• Driver alteration prevalence varies according to several demographic parameters – which remains to be explained

• Cancers harbouring identical alterations show large variations in response to the same targeted therapy demonstrating hidden and additional complexity
# Mutual exclusivity (1)

## Key findings: 97% of mutations mutually exclusive

<table>
<thead>
<tr>
<th># Single mutations</th>
<th>ALK</th>
<th>AKT</th>
<th>BRAF</th>
<th>EGFR</th>
<th>HER2</th>
<th>KRAS</th>
<th>MEK1</th>
<th>MET</th>
<th>NRAS</th>
<th>PIK3CA</th>
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<tr>
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<td>X</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<td>AKT1 (0)</td>
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<td>BRAF (9)</td>
<td>X</td>
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</tr>
<tr>
<td>EGFR (89)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HER2 (3)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS (114)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<td>1</td>
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</tr>
<tr>
<td>MEK1 (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MET AMP (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>NRAS (2)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3CA (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Number of patients with variants in indicated combination of genes, 3% (14/516)

Kris, ASCO 2011
Mutual exclusivity (2)

Concomitant actionable mutations and overall survival (OS) in EGFR-mutant non-small-cell lung cancer (NSCLC) patients (p) included in the EURTAC trial: EGFR L858R, EGFR T790M, TP53 R273H and EML4-ALK

Rosell, ESMO 2012

Chaft, Mol Cancer Ther 2011
Co-existence proof: at resistance

Systematic resistance to ALK inhibitors

Mechanisms responsible for EGFR-TKI resistance

Doebele, ASCO 2012; Sequist et al, Science Transl Med 2011
Distinct oncogenic drivers are found concomitantly in the same tumour, as proven for ALK, EGFR, MET, PIK3CA as well as for alterations of tumour suppressor genes.

HOWEVER:

• Molecular diagnosis remains strongly dependant of detection method sensitivity (clinical significance threshold?)

• Impact of co-existing genetic mutations, especially regarding tumour suppressor genes, remains to be explored

• No evidence to guide treatment choice in the context of multiple coexisting drivers is available
Heterogeneity of driver mutations

Temporal heterogeneity of tumour cells under selective pressure

Spatial heterogeneity of lesions

Table 2. Effect of First-Line Chemotherapy on EGFR Mutation Status Before and After Treatment in Plasma Samples From Patients With Stages IIIb to IV NSCLC (n = 264)

<table>
<thead>
<tr>
<th>Prechemotherapy</th>
<th>Wild Type</th>
<th>Mutated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Wild type</td>
<td>149</td>
<td>56.4</td>
<td>24</td>
</tr>
<tr>
<td>Mutated</td>
<td>54</td>
<td>20.5</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>76.9</td>
<td>61</td>
</tr>
</tbody>
</table>

NOTE. P < .001 (McNemar test). Abbreviation: NSCLC, non–small-cell lung cancer.
Conclusion 3

Distinct oncogenic drivers can therefore be multiple and heterogeneous, vary over time, under drug pressure and upon resistance to targeted agents

NEVERTHELESS:

• In selected populations, we have very good efficiency data regarding customised treatment to a single driver

• If we all believe combination targeted treatment will be promising, timing and schedules will be the next issues to solve
Translation in the clinic

TREATMENT TARGETS AS EXAMPLES

• ALK
• ROS
• RET
• BRAF
• HER2
• FGFR1
• KRAS
Making the best use of off-target activities of TKIs
Translation in the clinic: targeting ALK

<table>
<thead>
<tr>
<th>EML4-ALK</th>
<th>TFG-ALK</th>
<th>KIF5B-ALK</th>
</tr>
</thead>
<tbody>
<tr>
<td>E13;A20</td>
<td>E2;A20</td>
<td>E17;A20</td>
</tr>
<tr>
<td>E6;A20</td>
<td>E18;A20</td>
<td>E15;A20</td>
</tr>
<tr>
<td>E20;A20</td>
<td>E14;A20</td>
<td>E2;A20</td>
</tr>
<tr>
<td>E14;A20</td>
<td>E18;A20</td>
<td>E15;A20</td>
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<tr>
<td>E18;A20</td>
<td>E14;A20</td>
<td>E2;A20</td>
</tr>
<tr>
<td>E15;A20</td>
<td>E18;A20</td>
<td>E15;A20</td>
</tr>
</tbody>
</table>

Coiled-coil domain

Tyrosine kinase domain
Targeting ALK (2)

Prevalence in NSCLC: Retrospective Data

PREVALENCE AND CLINICAL OUTCOMES FOR PATIENTS WITH ALK GENE REARRANGEMENT IN EUROPE: PRELIMINARY RESULTS FROM THE EUROPEAN THORACIC ONCOLOGY PLATFORM LUNGSCAPE PROJECT

Blackhall, ESMO 2012

Higher prevalence in adenocarcinoma, never/light smokers and younger patients

Targeting ALK (3)

Crizotinib

Part 1: Dose escalation
- Cohort 1 (n=3): 50 mg QD
- Cohort 2 (n=4): 100 mg QD
- Cohort 3 (n=8): 200 mg QD
- Cohort 4 (n=7): 200 mg BID
- Cohort 5 (n=6): 300 mg BID
- Cohort 6 (n=9): 250 mg BID, MTD/RP2D

Part 2: Dose expansion
Molecularly enriched cohorts (c-MET, ALK, ROS1)
# Targeting ALK (3)

**Clinical trials program**

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Population</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROFILE 1001</td>
<td>ALL -&gt; ALK/MET -&gt; specific cohorts (cave ALK and ROS rearranged NSCLC)</td>
<td>Part 1: dose escalation&lt;br&gt;Part 2: molecular cohorts (NSCLC ALK+ from 2008)</td>
</tr>
<tr>
<td>PROFILE 1007</td>
<td>NSCLC ALK +; &gt; 1line</td>
<td>III vs docetaxel or pemetrexed (endpoint PFS)</td>
</tr>
<tr>
<td>PROFILE 1005</td>
<td>Not eligible for 1007 or crossover in 1007</td>
<td>II (endpoint ORR)</td>
</tr>
<tr>
<td>PROFILE 1014</td>
<td>Not pretreated NSCLC ALK+</td>
<td>III vs pem-platin (endpoint PFS)</td>
</tr>
</tbody>
</table>
Targeting ALK (4)

Activity of crizotinib

RR: 50-60%, duration of response: 40-50 weeks

PFS 1001: 10 months

Phase III randomized study of crizotinib versus pemetrexed or docetaxel chemotherapy in advanced, ALK-positive non-small cell lung cancer (NSCLC) (PROFILE 1007)

Shaw, ESMO 2012

Camidge, ASCO 2011; Riely, IASLC 2011
Targeting ALK (5)

Activity of HSP 90 Inhibitors

Mutated EGFR, EML4-ALK, MET, HER2, p-AKT, c-RAF are client proteins of HSP90

Responses in 4/8 patients with ALK (+), crizotinib-naive tumors

Katayama, Sci Transl Med 2012; Wong , ASCO 2011, Sequist JCO 2010
Translation in the clinic: targeting ROS

ROS1: Receptor tyrosine kinase of the insulin receptor family, little known about its specific function
ROS1 fusion with the transmembrane solute carrier protein SLC34A2 results in a constitutive kinase activity in a NSCLC cell line

Rikova, Cell 2007; Takeuchi, Nat Med 2011; Bergethon JCO 2012
Targeting ROS (2)

ROS1 fusions in 0.9% (13 out of 1,476) of NSCLC and 1.2% (13 out of 1,116) of adenocarcinoma

ROS1 fusions in 1.7% (all adenocarcinoma) of 1,073 NSCLC

Over-represented: female, adenocarcinoma, young (50), never smokers (stage IV?)

Crizotinib also inhibits ROS1

Berghethon JCO 2012; Takeuchi, Nat Med 2011
Targeting ROS (3)

Crizotinib expansion cohort (14 patients reported)
These results validate ROS1 as a therapeutic target in lung cancer

Bergethon JCO 2012, Riely ASCO 2012; Sequist ASCO 2012
Translation in the clinic: targeting RET

- Ligands: glial cell line-derived neurotrophic factor (GDNF) family

- Activation requires the formation of a multimere complex including the ligand, a GDNF-family receptor-α protein and RET
Fusion of KIF5B and RET identified in an adenocarcinoma of a young non-smoker by whole-genome and transcriptome sequencing.

- 6/319 (1.9%) RET fusion transcripts in adenocarcinoma from Japanese and 1/80 (1.3%) from Caucasian patients.

Capelletti, ASCO 2012; Young, Genome Res 2011; Kohno Nat med 2012
Targeting RET (3)

Kohno, Nat Med 2012; Capelletti, ASCO 2012
# Targeting RET (4)

<table>
<thead>
<tr>
<th>Study</th>
<th>Identification and verification method(s)</th>
<th>Ethnicity (n)</th>
<th>Percentage positive for KIF5B-RET</th>
<th>Variants identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohno et al.</td>
<td>Whole-transcriptome sequencing⁹</td>
<td>Japanese (30)</td>
<td>3.3</td>
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<tr>
<td></td>
<td>RT-PCR and Sanger sequencing</td>
<td>Japanese (289)</td>
<td>1.7</td>
<td>K15;R12, K16;R12, K23;R12, K24;R8</td>
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<tr>
<td></td>
<td></td>
<td>American (80)</td>
<td>1.3</td>
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<td></td>
<td></td>
<td>Norwegian (34)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td><strong>433</strong></td>
<td></td>
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<tr>
<td></td>
<td>Targeted capture and resequencing⁹</td>
<td>Not specified (24)</td>
<td>4.2</td>
<td>K15;R11, K15;R12, K16;R12, K22;R12</td>
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<tr>
<td></td>
<td>RT-PCR</td>
<td>Caucasian (121)</td>
<td>0.8</td>
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<tr>
<td></td>
<td></td>
<td>Korean (347)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Japanese (58)</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RET IHC and RT-PCR</td>
<td>Caucasian (92)</td>
<td>1.1</td>
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<tr>
<td></td>
<td></td>
<td>African American (5)</td>
<td>0.0</td>
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<td></td>
<td>Unknown (20)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td><strong>667</strong></td>
<td></td>
</tr>
<tr>
<td>Lipson et al.</td>
<td>IHC and FISH screen⁹</td>
<td>Japanese (1529)</td>
<td>0.9</td>
<td>K15;R12, K16;R12, K22;R12, K23;R12, K24;R11</td>
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<td>Ju et al.</td>
<td>Whole-genome and whole-transcriptome sequencing⁹</td>
<td>Korean (1)</td>
<td>100.0</td>
<td>K15;R12, K16;R12, K23;R12</td>
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<td></td>
<td>Whole-transcriptome sequencing (screen)</td>
<td>Korean (5)</td>
<td>20.0</td>
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<td></td>
<td>RT-PCR</td>
<td>Korean (15)</td>
<td>6.7</td>
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<td></td>
<td><strong>Total</strong></td>
<td></td>
<td><strong>2,650</strong></td>
<td></td>
</tr>
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</table>

No clinical validation of RET targeting

Pao, Nat Med 2012
Translation in the clinic: targeting HER2

Lung cancer that harbors a HER2 mutation:
Epidemiological characteristics and therapeutic perspectives

Mazières and Peters, ESMO 2012
Translation in the clinic: targeting BRAF

- BRAF mutations in 36 adenocarcinoma (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 2012
Targeting BRAF (2)

A Patient With BRAF V600E Lung Adenocarcinoma Responding to Vemurafenib

Kinase-Impaired BRAF Mutations in Lung Cancer Confer Sensitivity to Dasatinib

Banibrata Sen, Shaohua Peng, Ximing Tang, Heidi S. Erickson, Hector Galindo, Tuhina Mazumdar, David J. Stewart, Ignacio Wistuba, Faye M. Johnson

Gautschi, JTO 2012; Solit and Janne Nature 2012; Sen, Sci Transl Med 2012
Translation in the clinic: targeting FGFR1

SNP Array: ~10% of SCC Amplification

FISH ~22% of SCC Amplification

Weiss, Sci Transl Med. 2010
Targeting FGFR1 (2)

Some examples in early clinical trials:

**AP24534 (Ponatinib)** - BCR/ABL, PDGFR, VEGFR, FGFR

**AZD4547** - FGFR, VEGFR, PDGFR

**GJ398** – FGFR

**BIBF1120 (Intedanib)** - VEGFR, PDGFR, FGFR

**TKI258 (Dovitinib)** - FLT3, c-KIT, FGFR, VEGFR

**PD173074** - FGFR, VEGFR

Gozgit, Mol Cancer Ther 2012; Weiss, Sci Transl Med. 2010
Translation in the clinic: targeting KRAS pathway

Janne, ASCO 2012
Targeting KRAS pathway (2)

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR</th>
</tr>
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<tbody>
<tr>
<td>Pemetrexed$^1$</td>
<td>9%</td>
</tr>
<tr>
<td>Docetaxel$^1$</td>
<td>9%</td>
</tr>
<tr>
<td>Erlotinib (unselected)$^2$</td>
<td>9%</td>
</tr>
<tr>
<td>Erlotinib (EGFR mut)$^3,4$</td>
<td>70%</td>
</tr>
<tr>
<td>Crizotinib (ALK)$^5$</td>
<td>61%</td>
</tr>
<tr>
<td>Crizotinib (ROS1)$^6$</td>
<td>57%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>0%</td>
</tr>
<tr>
<td>Selumetinib + docetaxel</td>
<td>37%</td>
</tr>
</tbody>
</table>

Janne, Neal ASCO 2012
Targeting KRAS pathway (3)

Types of KRAS mutations

Lung Adenocarcinoma

Hainsworth, Clin Cancer Res 2008
Targeting KRAS pathway (4)

KRAS G12 mutation frequencies

CRC

NSCLC

RAS mutations and oncogenesis: Not all RAS mutations are created equally
Miller & Miller (2011) Front Genet 2:100
Targeting KRAS pathway (5)
A new strategy

A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response

Co-clinical results identify predictive genetic biomarkers that should be validated by interrogating samples from patients enrolled on the concurrent clinical trial, allowing to anticipate the results and generate clinically relevant hypotheses.

Chen, Nature 2012
Cancer Cell Can Survives in a Hostile Environment

Luo, Cell 2009
Conclusions

Everything has become largely more complex

PERSPECTIVES:

• For almost every single indentified driver, early trials with targeted agent are ongoing (phase I/II)

• The “NSCLC”-devoted trial will probably become a rare concept in the years to come

• Prospective molecularly-driven trials will require large international network of centers, political and economical support as well as a strong multidisciplinary collaboration
Thanks for your attention