Drawing the map: molecular characterization of NSCLC

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Disclosures

• Honoraria for advisory board/consultancy/speakers fee
  – Eli Lilly
  – Roche
  – Boehringer Ingelheim
  – Bristol-Myers Squibb
  – MSD
  – Amphera B.V.
  – Verastem
  – AstraZeneca

• Research funding department
  – Eli Lilly
  – Roche
  – Boehringer Ingelheim

• Patents pending
  – Tumour lysate antigen

• Stock owner
  – Amphera B.V. immunotherapy
Learning objective

- After this presentation, participants will be able to
  - identify molecular pathways that drive malignancy in advanced NSCLC
  - understand the importance of genetic testing in improving diagnosis and identifying opportunities for treatments
  - recognize the limited treatment options available for advanced squamous NSCLC
Question 1

Should molecular profiling be part of the diagnostic work-up in a patient with advanced squamous NSCLC who is a smoker?

1. Yes
2. No
First-line therapy with gefitinib prolongs PFS in patients with \textit{EGFR} mutation

**Overall**

\[ \text{HR} 0.74 \ (95\% \ CI 0.65–0.85) \quad p < 0.001 \]

Events: gefitinib 453 (74.4%); carboplatin + paclitaxel 497 (81.7%)

**EGFR-mutation-positive**

\[ \text{HR} 0.48 \ (95\% \ CI 0.36–0.64) \quad p < 0.001 \]

Events: gefitinib 97 (73.5%); carboplatin + paclitaxel 111 (86.0%)

**EGFR-mutation-negative**

\[ \text{HR} 2.85 \ (95\% \ CI 2.05–3.98) \quad p < 0.001 \]

Events: gefitinib 88 (96.7%); carboplatin + paclitaxel 70 (82.4%)

**Unknown \textit{EGFR} mutation status**

\[ \text{HR} 0.68 \ (95\% \ CI 0.58–0.81) \quad p < 0.001 \]

Events: gefitinib 268 (69.4%); carboplatin + paclitaxel 316 (80.2%)

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival.
ESMO Guidelines 2016

Non-squamous

Stage IV NSCLC

**ALK translocation**
- Crizotinib

**Molecular tests**
- No EGFR/ALK mutation
  - < 70 years and PS 2 or
  - > 70 years and PS 0–2

**EGFR mutation**
- Gefitinib
- Erlotinib
- ± bevacizumab
- Afatinib

**ALK**, anaplastic lymphoma kinase; **PS**, performance status.

ESMO Guidelines 2016

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**ALK, anaplastic lymphoma kinase; PS, performance status.**

Non-squamous

- **ALK translocation** → Crizotinib
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    - Gefitinib
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ALK, anaplastic lymphoma kinase; PS, performance status.

ESMO Guidelines 2016

Crizotinib as first-line therapy prolonged PFS in patients with advanced ALK-positive NSCLC

HR for progression or death in crizotinib group
0.45 (95% CI 0.35–0.60); p < 0.001*

* 2-sided stratified log rank test.

Tumour responses to crizotinib in ROS1-rearranged NSCLC

- ROS1 rearrangements represent a second molecular subgroup of NSCLC that can be targeted with crizotinib
- Response rates to crizotinib are high in ROS1-rearranged NSCLC

<table>
<thead>
<tr>
<th>Type of response (n = 50)</th>
<th>ROS1 cohort, number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Partial response</td>
<td>33 (66)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

- Duration of response was 17.6 months (95% CI 14.5−NR)
  - 64% of responses were ongoing at the time of data cutoff

NR, not reached; ROS1, ROS1 proto-oncogene receptor tyrosine kinase.

Case discussion

Second opinion: no treatment options?

- 65-year-old male
- Adenocarcinoma of the RUL
  - liver and left adrenal gland metastasis
  - EGFR testing negative
  - no ALK translocation
- 2013
  - started treatment with cisplatin + pemetrexed with partial response
  - progressive disease after 8 cycles of pemetrexed maintenance

RUL, right upper lobe of lung.

Courtesy of J. Aerts.
Case (continued)

- Started on docetaxel (75 mg/m²/3 weeks)
  - hospitalized for cardiac arrest after the second cycle
- Docetaxel discontinued
Question 2

What would you do?
1. BSC
2. Restart on another chemotherapy
3. Check mutation testing
4. Consider phase 1 study
5. Immunotherapy after PD-L1 testing
Case (continued)

- Check mutation testing
  - referring hospital tested for $EGFR$ in:
    - exon 19
    - exon 21

- NGS testing
  - $EGFR$ mutation positivity:
    - exon 18

NGS, next-generation sequencing.
Case (continued)

• 2014
  – started on erlotinib (150 mg/day) with a partial response

• 2016
  – progressive disease in liver and lung
Question 3

What would your next step be?

1. Start on immunotherapy with PD-L1 inhibitors
2. Restart chemotherapy
3. BSC
4. Perform new mutation testing
Case (continued)

- Additional liver biopsy and cfDNA (liquid biopsy) testing
  - T790M positivity
- Started on osimertinib (80 mg/day)
  - partial response up to present

Courtesy of J. Aerts.
Osimertinib vs platinum + pemetrexed in T790M-positive advanced NSCLC: PFS

Duration of PFS among patients with T790M-positive status after first-line EGFR-TKI therapy

EGFR-TKI, EGFR tyrosine kinase inhibitor.

Follow up targeted therapy: gefitinib in EGFR-positive patients

No difference in OS for gefitinib vs carboplatin + paclitaxel in patients with EGFR mutation status

OS, overall survival.

Acquired resistance also develops

- Patient example with resistance to ALK mutation and subsequent treatments can be found:
  - Shaw AT, et al. N Engl J Med. 2016;374:54-61 (Figure 1)
Performing NGS for a more comprehensive molecular screening

**Overall**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>11%</td>
</tr>
<tr>
<td>KRAS</td>
<td>29%</td>
</tr>
<tr>
<td>BRAF</td>
<td>2%</td>
</tr>
<tr>
<td>HER2</td>
<td>1%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>2%</td>
</tr>
<tr>
<td>ALK</td>
<td>5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>35%</td>
</tr>
<tr>
<td>Full WT</td>
<td>15%</td>
</tr>
</tbody>
</table>

**Adenocarcinoma**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>12%</td>
</tr>
<tr>
<td>KRAS</td>
<td>31%</td>
</tr>
<tr>
<td>BRAF</td>
<td>2%</td>
</tr>
<tr>
<td>HER2</td>
<td>1%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>2%</td>
</tr>
<tr>
<td>ALK</td>
<td>5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>32%</td>
</tr>
<tr>
<td>Full WT</td>
<td>15%</td>
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**Women**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>21%</td>
</tr>
<tr>
<td>KRAS</td>
<td>27%</td>
</tr>
<tr>
<td>BRAF</td>
<td>2%</td>
</tr>
<tr>
<td>HER2</td>
<td>1%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>3%</td>
</tr>
<tr>
<td>ALK</td>
<td>6%</td>
</tr>
<tr>
<td>Unknown</td>
<td>28%</td>
</tr>
<tr>
<td>Full WT</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Never smokers**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>44%</td>
</tr>
<tr>
<td>KRAS</td>
<td>9%</td>
</tr>
<tr>
<td>BRAF</td>
<td>3%</td>
</tr>
<tr>
<td>HER2</td>
<td>4%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>4%</td>
</tr>
<tr>
<td>ALK</td>
<td>14%</td>
</tr>
<tr>
<td>Unknown</td>
<td>13%</td>
</tr>
<tr>
<td>Full WT</td>
<td>9%</td>
</tr>
</tbody>
</table>

WT, wild type.

Survival of patients with drivers: targeted therapy versus no targeted therapy


Number at risk:

- Patients with oncogenic driver:
  - No targeted therapy: 205, 110, 64, 43, 20
  - Targeted therapy: 225, 143, 72, 36, 23
  - Patients with no driver: 250, 122, 59, 36, 23

Log-rank p < 0.001
Oncogenic drivers in NSCLC

Controversy
Parachute approach to evidence based medicine

Malcolm Potts, Ndola Prata, Julia Walsh, Amy Grossman

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done.

Sometimes it’s best just to jump in!
Question 3 (continued)

What is your next step?

1. **Start on immunotherapy with PD-L1 inhibitors**
2. Restart chemotherapy
3. BSC
4. New mutation testing
What is your next step?
1. Start on immunotherapy with PD-L1 inhibitors
2. Restart chemotherapy
3. BSC
4. New mutation testing
Immunotherapy may not be an effective treatment option in patients with an EGFR mutation.

Second-line nivolumab in non-squamous NSCLC: OS by subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients, n</th>
<th>Unstratified hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69–2.00)</td>
</tr>
<tr>
<td>Not detected</td>
<td>340</td>
<td>0.66 (0.51–0.86)</td>
</tr>
<tr>
<td>Not reported</td>
<td>160</td>
<td>0.74 (0.51–1.06)</td>
</tr>
</tbody>
</table>

What about squamous cell carcinoma?

IASLC, International Association for the Study of Lung Cancer; SqCLC, squamous cell lung cancer.


**EGFR + or ALK + < 5%**

Squamous NSCLC

Unknown oncogenic drivers or oncogenic drivers without proven treatments

The IASLC SqCLC education program

IASLC, International Association for the Study of Lung Cancer; SqCLC, squamous cell lung cancer.
ESMO Guidelines 2016

Squamous

Never or former-light smoker (< 15 pack/year)

Molecular test (ALK/EGFR)

Molecular test positive

Molecular test negative

Targeted therapy

Stage IV SCC

Age and PS

SCC, squamous cell carcinoma.

Conclusion

- Molecular profiling has increased the therapeutic potential in advanced NSCLC
- For the majority of patients, certainly for those with squamous cell NSCLC, targetable drivers are lacking
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