Update on Targeted Therapies of NSCLC

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Bled 2014
Systemic Therapy of Advanced NSCLC: Chemotherapy Range

- Cht improves survival rates by 1.5 mos (from 4.5 to 6.0 mos)
- Platinum doublets are standard
- **21st Century: Chemotherapy has reached a plateau in NSCLC, with novel treatment strategies urgently needed!**
  - third-gen platinum doublets
- Similar outcomes, RR from 20% to 30%, mPFS 3.5–5 months, mOS of 8–10 months
Evolution of NSCLC Subtyping from Histologic to Molecular Based

NSCLC as one disease

Li T et al. J Clin Oncol 2013
Hitting the Mark: Biomarker-driven Treatment Strategies

- Over 50% of NSCLC cases are linked to known molecular markers
- At least 10 known molecular markers in NSCLC

Mainly Adenocarcinoma

No mutation detected

- KRAS
- EML4-ALK - 4%
- EGFR - 17%
- NRAS
- IDH1
- CTTNB1
- HER2
- MET
- PIK3CA
- BRAF

Sequist LV et al., Ann Oncol. 2011
2004: Activating EGFR Mutations Discovered

- EGFR TKI- sensitizing mutations are present in 10-20% of NSCLC in Western population, mainly in adenocarcinomas, non-smokers, female population.

- Remarkable and rapid responses to 1st generation EGFR-directed TKIs.

Lynch et al. NEJM 2004; Paez et al. Science 2004
INTEREST: Gefitinib vs. Cht in Second-line Therapy: PFS Biomarkers

Overall N=1316
High EGFR-gene-copy number N=158
Low EGFR-gene-copy number N=179
EGFR protein expression positive N=258
EGFR protein expression negative N=87
EGFR mutation positive N=38
EGFR mutation negative N=229
K-RAS mutation positive N=47
K-RAS mutation negative N=203

HR (gefitinib vs docetaxel) and 95% CI

Favours gefitinib ←→ Favours docetaxel

Douillard et al, JCO 2009
First-line Gefitinib vs Carbo/Pacli in Clinically Selected pts with Advanced NSCLC in Asia (IPASS trial)

**Patients**
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB / IV disease

Gefitinib (250 mg / day)

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly#

1:1 randomisation

**Endpoints**

**Primary**
- Progression-free survival (non-inferiority)

**Secondary**
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

**Exploratory**
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

Carboplatin / paclitaxel was offered to gefitinib patients upon progression

Mok et al, NEJM 2009
IPASS: PFS in EGFR Mutation Positive and Negative Patients

<table>
<thead>
<tr>
<th>EGFR mutation positive</th>
<th>EGFR mutation negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (n=132)</td>
<td>Gefitinib (n=91)</td>
</tr>
<tr>
<td>Carboplatin / paclitaxel (n=129)</td>
<td>Carboplatin / paclitaxel (n=85)</td>
</tr>
<tr>
<td>HR (95% CI) = 0.48 (0.36, 0.64)</td>
<td>HR (95% CI) = 2.85 (2.05, 3.98)</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Treatment by subgroup interaction test, p<0.0001

Mok T et al, NEJM 2009
## TKIs vs. Chemotherapy in EGFR-mutated Advanced NSCLC

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Comparison</th>
<th>ORR (%)</th>
<th>PFS (Mos)</th>
<th>HR</th>
<th>OS (Mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS**</td>
<td>Gefitinib v. Carbo/Pac</td>
<td>71 vs. 47%</td>
<td>9.5 v. 6.3</td>
<td>0.48 (0.36-0.64)</td>
<td>21.6 vs. 21.9</td>
</tr>
<tr>
<td>(n=261)</td>
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<tr>
<td>WJOTG</td>
<td>Gefitinib v. Cis/Doce</td>
<td>*62 vs. 32%</td>
<td>9.2 v. 6.3</td>
<td>0.49 (0.34-0.71)</td>
<td>35.5 vs. 38.8</td>
</tr>
<tr>
<td>(n=172)</td>
<td></td>
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<tr>
<td>NEJ002</td>
<td>Gefitinib v. Carbo/Pac</td>
<td>74 vs. 31%</td>
<td>10.8 v. 5.4</td>
<td>0.30 (0.22-0.41)</td>
<td>27.7 vs. 26.6</td>
</tr>
<tr>
<td>(n=230)</td>
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<tr>
<td>EURTAC</td>
<td>Erlotinib v. Chemotherapy</td>
<td>*58 vs. 15%</td>
<td>9.7 v. 5.2</td>
<td>0.37 (0.25-0.54)</td>
<td>19.3 vs. 19.5</td>
</tr>
<tr>
<td>(n=174)</td>
<td></td>
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</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib v. Carbo/Gem</td>
<td>*83 vs. 36%</td>
<td>13.1 v. 4.6</td>
<td>0.16 (0.10-0.26)</td>
<td>22.7 vs. 28.9</td>
</tr>
<tr>
<td>(n=165)</td>
<td></td>
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</tr>
<tr>
<td>LUX-lung 3</td>
<td>Afatinib v. Cis/Pem</td>
<td>*61 vs. 22%</td>
<td>*13.6 v. 6.9</td>
<td>0.47 (0.34-0.65)</td>
<td>30.3 vs. 26.2</td>
</tr>
<tr>
<td>(n=345)</td>
<td>56 vs. 23%</td>
<td>11.1 v. 6.9</td>
<td>0.58 (0.34-0.65)</td>
<td>28.1 vs. 28.2</td>
<td></td>
</tr>
<tr>
<td>Lux-Lung 6</td>
<td>Afatinib v. Cis/Gem</td>
<td>67 vs. 23%</td>
<td>11.0 v. 5.6</td>
<td>0.28 (0.20-0.39)</td>
<td>22.11 vs. 22.24</td>
</tr>
<tr>
<td>(n=364)</td>
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</tbody>
</table>

* Del 19, L858 mu, ** Post-hoc analysis of EGFR mutant patients
First discovered in 2007, EML4-ALK is now a validated therapeutic target in a small but significant subset of NSCLC patients.
# Notable Trials ALK Tyrosine Kinase Inhibitor

<table>
<thead>
<tr>
<th>Study (Phase) Author</th>
<th>Study arms</th>
<th>No. of pts</th>
<th>RR (%)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROFILE 1001 (I)1</td>
<td>Crizotinib</td>
<td>149</td>
<td>60.8</td>
<td>9.7</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.7 FL</td>
<td>Not yet reached 74% at 1y</td>
</tr>
<tr>
<td>PROFILE 1005 (II)2</td>
<td>Crizotinib</td>
<td>261</td>
<td>60</td>
<td>8.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20*</td>
<td>NR</td>
</tr>
<tr>
<td>PROFILE 1007 (III)3</td>
<td>Crizotinib Cht. Pemetrexed Docetaxel</td>
<td>347</td>
<td>65 20* 29 7</td>
<td>7.7 3.0 4.2 2.6</td>
<td>0.49 (0.37 – 0.64) 20.3 22.8 1.02 (0.68 – 1.54)</td>
</tr>
</tbody>
</table>

Driver Mutations with Predicted Likelihood of Response to Current Targeted Therapies

<table>
<thead>
<tr>
<th>Oncogene Mutation Prevalence</th>
<th>Mutation-Predicted Response</th>
<th>Predicted RR</th>
<th>Predicted mPFS (months)</th>
<th>Predicted mOS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Sensitive to EGFR</td>
<td>erlotinib</td>
<td>9-14 mos</td>
<td>19-35 mos</td>
</tr>
</tbody>
</table>

- Targeted therapy based on the presence of EGFR mutations and ALK gene rearrangements has become a standard practice.
- EGFR and ALK testing is now recommended for all advanced NSC NSCLC, in order to guide treatment decisions, with most of the countries implementing diagnostic tests after approval of targeted drugs.

Asians?
### Phase III Trials Comparing Cht with or without Targeted Therapy in Biomarker Unselected NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Response rate</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLEX&lt;sup&gt;1&lt;/sup&gt; (EGFR IHC+ NSCLC)</td>
<td>CV + cetuximab CV</td>
<td>35 28</td>
<td>4.8 4.8</td>
<td>11.3* 10.1</td>
</tr>
<tr>
<td>BMS 009&lt;sup&gt;2&lt;/sup&gt; (All NSCLC)</td>
<td>CT + cetuximab CT</td>
<td>26 17</td>
<td>4.4 4.2</td>
<td>9.6 8.3</td>
</tr>
<tr>
<td>ECOG &lt;sup&gt;3&lt;/sup&gt;</td>
<td>CarboP + beva CarboP</td>
<td>35 15</td>
<td>6.2* 4.5</td>
<td>12.3* 10.3</td>
</tr>
<tr>
<td>AVAIL &lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>CG + beva (7.5 mg)</td>
<td>34.1 30.4 20.1</td>
<td>6.8* 6.6* 6.2</td>
<td>13.6 13.4 13.1</td>
</tr>
<tr>
<td></td>
<td>CG + beva (15 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CG + placebo</td>
<td></td>
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</tbody>
</table>

* = significant

The efficacy of targeted therapy without identifiable target is limited!

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Unresolved Issues regarding Biomarker-driven Therapies

? Why biomarker-driven therapies should preferentially be used as first-line therapy

? How to overcome resistance to biomarker-driven therapies

? Treatment beyond progression
Why Biomarker-driven Therapy should be used as First-line Therapy

- There are no comparative data between FL and SL EGFR TKIs.

> However, there is a strong believe that the most effective drugs are to be used in first line, thus ensuring benefit to all patients (approx. 25% of NSCLC pts are lost between FL and SL therapy!)

![Diagram of EGFR mutation-positive lung cancer progression](image_url)

Adopted from Mok T et al. JCO 2013
Resistance to EGFR- and ALK- inhibitors

- Despite marked activity of EGFR TKIs and crizotinib resistance develops in one to two year time.
- Genetic alterations of target (second-site mutations, T790M), activation of aberrant signalling pathways, histologic changes (SCLC transformation).
- Various drugs and their combinations targeted to the resistance pathways are under development.
Phase I Study of 3\textsuperscript{rd} generation TKI (AZD9291) in EGFR-Mutant Patients Beyond Progression on EGFR TKI

- **Population:** patients with target lesion data (n=24)

- **Dose (mg/day) received noted on bar**

  - Promising clinical activity and tolerability with mostly G1/2 rash and diarrhoea

- **Discontinued treatment**

  - D

  - PD

  - SD

  - PR

  - T790M negative

  - T790M positive

  - Mutation status unknown

Ranson M, et al. ECCO 2013
Response to Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer (NSCLC).

Afatinib+Cetuximab in EGFR-mutant NSCLC with Acquired Resistance to TKI: Phase 2

- Data from 100 eligible patients
- Majority of patients with acquired resistance to erlotinib and gefitinib derived benefit from afatinib + cetuximab
- ORR 32%, CB 75% in heavily pretreated population with T790M-positive and T790M-negative tumours

\[ \text{mPFS} = 4.67 \text{m} \]
Clinical Benefit of Continuing Crizotinib beyond Progression in ALK-positive NSCLC

- Targeted therapy beyond progression on targeted therapy might represent the best approach in oncogene-driven NSCLC as well!

Sai-Hong I. Ou et al, WCLC Sydney 2013
Optimising EGFR TKI treatment duration: upcoming data

**ASPIRATION (Phase II, Asia)**

- Advanced NSCLC with *EGFR* mutation (n=208)
- Erlotinib
- PD by RECIST
- Erlotinib
- PD by physician discretion

**Primary endpoint**

PFS 1

**IMPRESS (Phase III, Europe/Japan/Asia)**

- Advanced NSCLC with *EGFR* mutation (n=287)
- First-line gefitinib
- PD by RECIST
- Gefitinib + pemetrexed/cisplatin
- Pemetrexed/cisplatin

**Primary endpoint**

PFS

1. NCT01310036
2. NCT01544179
Local therapy with continuation of TKI can improve disease control rate and delay start of another systemic therapy in oligometastatic progressive disease!
Future Directions

- Recognition of new oncogene-drivers
- Development of novel biomarker-targeted agents
- Harnessing the immune system
- Treatment tailored to cancer evolution, a move from „individualized“ to so called „precision medicine“
# New Targeted Agents in Development

<table>
<thead>
<tr>
<th>Target</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 amplification, mutations</td>
<td>Afatinib, Neratinib, Dacomitinib</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>Vemurafenib, dabrafenib</td>
</tr>
<tr>
<td>RET re-arrangements</td>
<td>Vandetanib, Sorafenib, Sunitinib</td>
</tr>
<tr>
<td>KRAS mutations</td>
<td>Selumetinib, Trametinib</td>
</tr>
<tr>
<td>PI3KCA mutations</td>
<td>GDC-0941, XL147</td>
</tr>
<tr>
<td>MET/HGF amplification</td>
<td>Onartuzumab, Rilotumumab, Tivantinib,</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Brivanib</td>
</tr>
<tr>
<td>DDR2</td>
<td>Dasatinib</td>
</tr>
</tbody>
</table>
Compared to adenocarcinoma, there are NO proven molecularly targeted therapies for squamous cell carcinoma and fewer potential targets.
Cancer Immunotherapy: Balance between Inhibitory and Stimulatory Receptors

T cell targets for modulating activity

Activating Receptors
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Receptors
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agonistic Antibodies

Blocking Antibodies

Mellman Nature 2011; Pardoll Nat Rev Cancer 2012
MPDL3280A (anti-PDL1) Phase Ia: Potential Predictors of Activity – NSCLC

<table>
<thead>
<tr>
<th>Diagnostic Population (n=53)</th>
<th>ORR % (n/n)</th>
<th>PD Rate % (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3</td>
<td>83% (5/6)</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>IHC 2/3</td>
<td>46% (6/13)</td>
<td>23% (3/13)</td>
</tr>
<tr>
<td>IHC 1/2/3</td>
<td>31% (8/26)</td>
<td>38% (10/26)</td>
</tr>
<tr>
<td>All Patients</td>
<td>23% (12/53)</td>
<td>40% (21/53)</td>
</tr>
</tbody>
</table>

Response by smoking status (ORR)

- Former/current smokers: 26%
- Never smokers: 10%

BIRCH phase II study (GO28754; NCT02031458)

PD-L1 positive locally advanced or metastatic NSCLC*  
ECOG PS 0–1

Primary endpoint: ORR

Treatment period  
MPDL3280A 1200mg iv q3w x16 cycles (≈1y)

Patients with CR/PR/SD followed every 12 weeks until PD

Horne, et al. WCLC 2013
Cancer Evolution: The Final Frontier of Precision Medicine?

“Tumor Darwinism”: Reducing sensitive clones by therapy permits unopposed growth of less fit resistant clones or emergence of a new clone.

Pooled cDNA genomic analysis from liquid biopsies might allow us to follow cancer clonal evolution during the disease course and tailor biomarker-driven therapy accordingly.
Because of the low frequency of the majority of these aberrations, a single master protocol assigning patients to different agents based on molecular characteristics appears to be the ideal approach.
We are getting faster!

Median progression free and overall survival (mos)

1970s

1970s

1990-2005

2005-2010

2010 ➔

One size fits all

Individualized Cht

Biomarker-driven therapy

EGFR – directed FKIs
22-35 mos

ALK
20-24 mos

mPFS
10-13 mos

Maintenance therapy
11-13 mos

Histology – driven cht
11 mos

P-based doublets
3rd gen.
8-10 mos

Cht
6-8 mos

BSC
2-4 mos

directed therapy
20-24 mos

mPFS
7-10 mos

10

11

14

13

4

8

10

11

Thank you for your attention!

Precision medicine