ASCO 2013 Lung Cancer Highlights

• How to improve outcome in stage III NSCLC?
• Customized chemotherapy for NSCLC
• Maintenance treatment for advanced non-squamous NSCLC
• Targeted treatments

How to improve outcome in stage III NSCLC?

• Vaccination?
• More irradiation?
• Adding surgery to radiotherapy?
• Adding radiotherapy to surgery?

START trial: phase III study of L-BLP25 immunotherapy for unresectable stage III NSCLC

Primary endpoint: Overall survival

<table>
<thead>
<tr>
<th>Condition</th>
<th>L-BLP25 (m)</th>
<th>Placebo (m)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>25.6</td>
<td>22.3</td>
<td>0.88 (0.75–1.03)</td>
<td>0.123</td>
</tr>
<tr>
<td>Concurrent chemo/RT</td>
<td>30.8</td>
<td>20.6</td>
<td>0.78 (0.64–0.95)</td>
<td>0.029</td>
</tr>
<tr>
<td>Sequential chemo/RT</td>
<td>19.4</td>
<td>24.6</td>
<td>1.12 (0.87–1.44)</td>
<td>0.38</td>
</tr>
</tbody>
</table>
**Standard-dose (60Gy) vs high-dose (74Gy) chemoradiotherapy for stage III NSCLC**

**Objective:** To evaluate OS with high-dose vs. standard-dose conformal radiation therapy with concurrent chemotherapy in patients with stage III NSCLC.

- **Participants:** 341 patients
- **Treatment:**
  - Standard-dose (60 Gy) radiotherapy + chemotherapy
  - High-dose (74 Gy) radiotherapy + chemotherapy

**Primary endpoint:** Overall survival

- Surgery was possible in 78% of patients with stage III NSCLC.
- No surgery: 81% of patients were resectable.
- 50% were ECOG PS 0-1.

**Results:**
- Overall survival:
  - Surgery: 17.3 months
  - No surgery: 14.9 months
  - HR: 0.866 (p = 0.009)

**Role of surgery in T1-3N2M0 NSCLC**

**Objective:** To investigate the effect on OS of the addition of surgery among patients with stage III NSCLC.

- **Participants:** 464 patients
- **Treatment:**
  - Surgery + chemotherapy
  - No surgery

**Primary endpoint:** Overall survival

- Surgery arm was better compared to the bimodality arm.
- HR for stage III NSCLC:
  - Surgery: 0.930
  - No surgery: 0.767
  - p value: 0.0319

**Role of surgery in stage IIIA/N2 NSCLC**

**Objective:** To investigate the effect on OS of the addition of surgery among patients with stage IIIA/N2 NSCLC treated with induction chemotherapy followed by surgery.

- **Participants:** 219 patients
- **Treatment:**
  - Surgery
  - No surgery

**Primary endpoint:** Event-free survival

- At 3rd interim analysis the futility boundary was crossed, trial stopped.
Role of preoperative RT in stage IIIA/N2 NSCLC (SAKK 16/00)

- Radiotherapy did not improve EFS or OS, nor did it reduce the local failure rate
- However, OS rates are high with a median of 27 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resected pts</th>
<th>R0-resection</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT+RT-S</td>
<td>82%</td>
<td>90%</td>
<td>0.91 (0.65–1.26)</td>
</tr>
<tr>
<td>CT+S</td>
<td>81%</td>
<td>80%*</td>
<td>1.15 (0.79–1.67)</td>
</tr>
</tbody>
</table>

* R1-R2 resections received PORT

How to improve outcome in stage III NSCLC?

- Vaccination? Not yet
- More irradiation? No
- Adding surgery to radiotherapy? No
- Adding radiotherapy to surgery? No

Customized chemotherapy for NSCLC

- ERCC1-IHC
- RRM1 and ERCC1 protein expression
- BRCA1 and RAP80 mRNA expression

**Phase II trial of customized adjuvant chemotherapy in resected NSCLC (TASTE trial)**

**Control**

- Observation

**Experimental**

- ERCC1/IHC positive
- Observation
- ERCC1 IHC negative
- Cis + Pem (4x)

**Key results**

- ERCC1 was positive in 38 patients (19 in each arm), EGFR mutation was identified in 10 patients (3 in control arm, 7 in customised arm)
- Feasibility was demonstrated with all patients starting therapy within 2 months of surgery

**Key conclusions**

- Although the feasibility of a national biology-driven trial in the adjuvant setting study was demonstrated, the study was cancelled due to the unexpected unreliability of the ERCC1 IHC read-out

**Phase III trial of molecular analysis-directed chemotherapy for advanced NSCLC**

- Previously untreated NSCLC
- PS 0-1
- RRM1 and ERCC1 determination by AQUA

**Primary endpoint:** PFS

N=275

**Objective:** to investigate feasibility of using ERCC1 and RRM1 as predictive markers for response to platinum agents and gemcitabine in patients with advanced NSCLC

**RNM1 low**

ERCC1 low

Gemci + Carbo

Doc + Carbo

**RNM1 high**

ERCC1 low

Gemci + Doc

Doc + VRB

**ERCC1 high**

Gemci + Doc

Doc + VRB

**Control**

- Cis + Pem (4x)

**Experimental**

- ERCC1/IHC positive
- Observation
- ERCC1 IHC negative
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**Objectives**

- To investigate feasibility of using ERCC1 and RRM1 as predictive markers for response to platinum agents and gemcitabine in patients with advanced NSCLC

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**Primary endpoint:** PFS

N=275
Phase III trial of molecular analysis-directed chemotherapy for advanced NSCLC

**Objective:** To investigate feasibility of using BRCA1 and RAP80 mRNA expression as predictive markers for response to platinum and taxane chemotherapy in patients with advanced NSCLC.

**Primary endpoint:** PFS

Planned interim-analysis on 279 pts

**Table:**

| Patients with 
<table>
<thead>
<tr>
<th>Median PFS (mo)</th>
<th>12.52 (11.5-16.6)</th>
<th>10.75 (10.0-13.0)</th>
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<tbody>
<tr>
<td>Patients censored (%)</td>
<td>66.5 (63.0-69.8)</td>
<td>70.5 (66.2-74.8)</td>
</tr>
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<td>Median PFS (mo)</td>
<td>9.30 (6.4-12.0)</td>
<td>7.30 (5.6-9.7)</td>
</tr>
<tr>
<td>p-value (Log-rank Test)</td>
<td>0.030</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**HR 1.36 (P <.05)**

Cis-Doc may not be optimal control for BRCA1 customization (?)

**Phase III of chemotherapy customization based on BRCA1-RAP80 expression (BREC)**

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**HR 1.36 (P <.0001)**

Cis-Doc may not be optimal control for BRCA1 customization (?)
Customized chemotherapy for NSCLC

- Phase III trials of chemo-customization are feasible, but have not yet resulted in improved outcomes.
- A patient with NSCLC is more than the molecular profile of the tumour!!!
**PointBreak trial: 2 different maintenance regimens** (Carbo+Pem+Bev vs Carbo+Pacli+Bev)

- **Objective:**
  - Investigate the correlation of biomarkers with OS, PFS and RR in the PointBreak study.

- **Induction (4 cycles):**
  - Carbo + Pemetrexed + Bevacizumab
  - Paclitaxel + Pemetrexed + Bevacizumab

- **Maintenance until PD:**
  - Carbo + Paclitaxel
  - Bevacizumab
  - Pemetrexed + Bevacizumab

- **Primary endpoint:** OS

- **Secondary endpoints:**
  - PFS, TTP, ORR, PRO, safety

- **Exploratory analyses:**
  - OS and PFS – age subgroups

- **Results:**
  - No differences for any of the secondary endpoints (PFS, OS, RR)
  - The primary endpoint (G4PFS) was not met (3.9m vs 2.9m; HR 0.83, P = 0.08)

- **Conclusion:**
  - No unexpected toxicities and both regimens demonstrated tolerability
  - Maintenance until PD

---

**Maintenance in non-squamous NSCLC:** lack of consistency?

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (m)</th>
<th>HR</th>
<th>Median OS (m)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>4.2 ± 1.5</td>
<td>0.86</td>
<td>10.1 ± 2.5</td>
<td>0.79</td>
</tr>
<tr>
<td>KRAS</td>
<td>6.1 ± 1.5</td>
<td>0.89</td>
<td>13.1 ± 1.3</td>
<td>1.03</td>
</tr>
<tr>
<td>ALK</td>
<td>5.6 ± 1.3</td>
<td>0.79</td>
<td>14.6 ± 1.5</td>
<td>0.78</td>
</tr>
<tr>
<td>ROS1</td>
<td>6.5 ± 1.2</td>
<td>0.58</td>
<td>15.9 ± 1.6</td>
<td>0.80</td>
</tr>
<tr>
<td>ROS2</td>
<td>4.4 ± 1.2</td>
<td>0.63</td>
<td>10.5 ± 1.1</td>
<td>1.07</td>
</tr>
<tr>
<td>PDK1</td>
<td>6.0 ± 1.5</td>
<td>0.80</td>
<td>12.6 ± 1.4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*P < 0.005

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**Translational research analysis of PointBreak trial in patients with nonsquamous NSCLC**

- **Objective:**
  - Investigate the correlation of biomarkers with OS, PFS and RR in the PointBreak study.

- **Specimens assessed using IHC (TS, TTF-1 and FR) and EGFR mutation status:**
  - Evaluable biomarker data for at least one assay were available for 211 patients

- **Results:**
  - The primary endpoint (G4PFS) was not met (3.9m vs 2.9m; HR 0.83, P = 0.08)
  - There were no differences for any of the secondary endpoints (PFS, OS, RR)
  - The primary endpoint (G4PFS) was not met (3.9m vs 2.9m; HR 0.83, P = 0.08)

- **Conclusion:**
  - There were no differences for any of the secondary endpoints (PFS, OS, RR)
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- **Conclusion:**
  - The primary endpoint (G4PFS) was not met (3.9m vs 2.9m; HR 0.83, P = 0.08)
Maintenance treatment for advanced non-squamous NSCLC

- Pemetrexed as preferred platinum partner in TTF-1 positive NSCLC
- Maintenance?

Targeted treatments for NSCLC

- EGFR-TKI
- Immunotherapy
- New targets

LUX-Lung 6: afatinib vs cisplatin + gemcitabine as 1st-line treatment for EGFR-mutation+ NSCLC

Objective: To compare the efficacy and safety of first-line treatment with afatinib versus gemcitabine+cisplatin in Asian patients with EGFR mutation-positive stage IIIB/IV lung adenocarcinoma.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ethnicity</th>
<th>EGFR-TKI</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (subgroup)</td>
<td>asian</td>
<td>Gefitinib</td>
<td>Cis + Doc (6x)</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>asian</td>
<td>Gefitinib</td>
<td>Cis + Doc (6x)</td>
</tr>
<tr>
<td>NEJ002</td>
<td>asian</td>
<td>Gefitinib</td>
<td>Carbo + Pacli (6x)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>asain</td>
<td>Erlotinib</td>
<td>Carbo + Gemci (4x)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>caucasian</td>
<td>Erlotinib</td>
<td>Cis / Carbo + Doc / Gemci (4x)</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>mixed</td>
<td>Afatinib</td>
<td>Cis + Pem (6x)</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>asain</td>
<td>Afatinib</td>
<td>Cis + Gemci (6x)</td>
</tr>
</tbody>
</table>

Primary endpoint: PFS

Phase III trials of 1st line EGFR-TKI vs chemo in EGFR mutation positive NSCLC

Objective: To evaluate erlotinib versus docetaxel in Japanese patients with NSCLC previously treated with ≥1 chemotherapy.

<table>
<thead>
<tr>
<th>Trial</th>
<th>EGFR-mutation</th>
<th>RR (%)</th>
<th>PFS (m)</th>
<th>HR PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (subgroup)</td>
<td>19Del/L858R + other (8%)</td>
<td>71 vs 47</td>
<td>7.6 vs 6.0</td>
<td>0.58</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>19Del/L858R</td>
<td>54 vs 29</td>
<td>6.3 vs 6.0</td>
<td>0.89</td>
</tr>
<tr>
<td>NEJ002</td>
<td>19Del/L858R</td>
<td>73 vs 54</td>
<td>10.3 vs 8.4</td>
<td>0.30</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>19Del/L858R</td>
<td>60 vs 35</td>
<td>16.7 vs 6.6</td>
<td>0.16</td>
</tr>
<tr>
<td>EURTAC</td>
<td>19Del/L858R</td>
<td>56 vs 30</td>
<td>9.5 vs 5.0</td>
<td>0.57</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>19Del/L858R + other (11%)</td>
<td>52 vs 23</td>
<td>11.1 vs 6.9</td>
<td>0.26</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>19Del/L858R + other (11%)</td>
<td>57 vs 23</td>
<td>11.0 vs 6.6</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Primary endpoint: Progression-free survival

DELTA trial: phase III study of erlotinib versus docetaxel as 2nd or 3rd line therapy

Objective: To evaluate erlotinib versus docetaxel in Japanese patients with NSCLC previously treated with ≥1 chemotherapy.

- Advanced stage IIIB/IV NSCLC
- 1-2 previous chemotherapy regimens including at least 1 platinum agent
- ECOG PS 0-2

Primary endpoint: Progression-free survival
DELTA trial: phase III study of erlotinib versus docetaxel as 2nd or 3rd line therapy

**Objective:** to evaluate erlotinib versus docetaxel in Japanese patients with NSCLC (non-squamous) treated with 1st chemotherapy

- Advanced stage IIIb/IV NSCLC
- ≥1 previous chemotherapy regimens including at least 1 platinum agent
- ECOG PS 0-2
- ≥1-2 previous chemotherapy
- Advanced stage IIIB/IV NSCLC

**Primary endpoints:**
- Progression-free survival in all adenocarcinoma
- Overall survival (EGFR unselected)

**Erlotinib 150 mg/day**

<table>
<thead>
<tr>
<th>Erlotinib</th>
<th>Docetaxel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR wild type</td>
<td>73 %</td>
<td>60 %</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>87 %</td>
<td>21 %</td>
</tr>
<tr>
<td>Not examined</td>
<td>12 %</td>
<td>19 %</td>
</tr>
</tbody>
</table>

No stratification or information regarding the prior lines of treatment

---

DELTA trial: phase III study of erlotinib versus docetaxel as 2nd or 3rd line therapy

**Primary endpoint:** Progression-free survival

**Overall survival (EGFR unselected)**

<table>
<thead>
<tr>
<th>Erlotinib</th>
<th>Docetaxel</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR wild type</td>
<td>1.3 m</td>
<td>2.0 m</td>
<td>0.122</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>0.9 m</td>
<td>1.4 m</td>
<td>0.086</td>
</tr>
<tr>
<td>EGFR unselected</td>
<td>14.8 m</td>
<td>12.2 m</td>
<td>0.907</td>
</tr>
</tbody>
</table>

- Relatively small trial with potential imbalances between treatment arms
- Erlotinib failed to show significant PFS advantage over docetaxel as 2nd or 3rd line therapy in EGFR-selected NSCLC
- While PFS was significantly longer in docetaxel than erlotinib in EGFR wild-type tumours, the difference did not translate into OS in this pragmatic trial

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DELTA trial: phase III study of erlotinib versus docetaxel as 2nd or 3rd line therapy

**Galaxy-1: docetaxel ± ganetespib (HSP-90 inhibitor) as 2nd line for lung adenocarcinoma**

**Objective:** to investigate safety and efficacy of the second generation heat shock protein 90 inhibitor, ganetespib, in patients with advanced lung adenocarcinomas

- Incurable or metastatic solid tumours
- Elevated LDH or KRAS 

- Advanced adenocarcinomas
- One prior systemic treatment
- ECOG PS 0-1

**Primary endpoints:**
- Progression-free survival in patients with elevated LDH or KRAS 

**MPDL3208A, an engineered PD-L1 antibody, locally advanced or metastatic NSCLC**

**Objective:** to determine recommended Phase II dose of the human engineered PD-L1 antibody, MPDL3208A, in patients with advanced squamous or non-squamous NSCLC

**Open-label, Phase Ia**

**Primary endpoints:** safety and ORR

| MPDL3208A | 1-2 mg/kg q3w 16 cycles |

*Engineered specifically to avoid killing of activated T-cells*
MPDL3280A, an engineered PD-L1 antibody, locally advanced or metastatic NSCLC

Tumor burden over time (NSCLC patients)

• Treatment with MPDL3280A was well tolerated (no grade 3-5 pneumonitis-related events or treatment-related death), and no dose-limiting toxicities up to 20 mg/kg
• Responses are ongoing in all responders in both squamous and non-squamous NSCLC
• PD-L1 tumour status correlated with higher response to MPDL3280A

LUME Lung-1 trial: docetaxel ± nintedanib in NSCLC progressing after 1st-line chemotherapy

Nintedanib: oral angiokinase inhibitor targeting VEGFR 1–3, FGFR 1–3, and PDGFR α/β as well as RET

Primary endpoint: PFS
Secondary endpoints: OS in the total population & OS in adenocarcinoma

Overall survival in all patients
Overall survival in adenocarcinoma

• LUME-Lung 1 met its primary endpoint: nintedanib in combination with docetaxel significantly prolonged PFS for all patients regardless of histology
• A significant improvement in OS was demonstrated in patients with adenocarcinoma
• Nintedanib plus docetaxel had a manageable safety profile with no unexpected safety findings

Targeted treatments for NSCLC

• EGFR-TKI: nothing new
• Immunotherapy: promising, but …needs confirmation
• New targets: promising, but …needs confirmation