A randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous Non-Small Cell Lung cancer (NSq-NSCLC) : LBA41_PR

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Disclosure

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ClinicalTrials.gov Identifier: NCT01282151
Background

Pemetrexed cisplatin is superior to gemcitabine cisplatin in Non-squamous NSCLC.

Docetaxel cisplatin is an active regimen for 1st line NSCLC.

In Japan Docetaxel is used in 60mg/m²/3 week dose.

Docetaxel 60mg/m² + Cisplatin q3 week was not inferior to Docetaxel 75mg/m² + Cisplatin q3 week while showing lower toxicities.
TRAIL

Chemo-naïve
Stage IV
Non-squamous
NSCLC

R

1:1

Docetaxel 60 mg/m²
Cisplatin 70 mg/m²
3 weekly (DP)

Pemetrexed 500 mg/m²
Cisplatin 70 mg/m²
3 weekly (AP)

Pemetrexed
or
EGFR-TKI
or
Docetaxel

up to 4 cycles

up to 4 cycles
Statistical analysis

Median PFS of Pem-Cis: 6.4 months in east Asian
  - Yang CH, JTO 2010;5(5):688
compared to 5.3 months in all ethnic patients.
  - Scagliotti GV, JCO 2008;26:3543.

Expected median PFS of Pem-Cis regimen = 6.4 months.
Non-inferiority margin = 1.5 months
Hazard ratio = 1.3
One sided significance level : 0.025, Power : 80%
N=281 * 2 = 562
TRAIL

Chemo-naïve Stage IV Non-squamous NSCLC N=562

Stratification factors
- ECOG 0-1 vs. 2
- Sex M vs. F

Biomarkers
- Genomic DNA
- Paraffin Tissue for available pts

Response evaluation after 2 and 4 cycles
If not progressed, f/u every 8~10 wks

Primary endpoint
- PFS

Secondary endpoints
- Response Rate by RECIST v 1.1
- OS
- Safety

Docetaxel 60 mg/m²
Cisplatin 70 mg/m²
3 weekly (DP)

Pemetrexed 500 mg/m²
Cisplatin 70 mg/m²
3 weekly (AP)

1:1

up to 4 cycles

Pemetrexed or EGFR-TKI or Docetaxel

up to 4 cycles

26-30 September 2014, Madrid, Spain
Inclusion Criteria

Age ≥ 18 years
ECOG Performance status: 0~2
Non-Squamous cell lung cancer
Stage IV or IIIB unable to receive curative radiation treatment or relapsed after Surgery or Radiation treatment
No prior Chemotherapy
Measurable lesion according to RECIST version 1.1
Adequate marrow, hepatic and renal function
Exclusion Criteria

- Activating EGFR mutation
- Hypersensitivity to Taxanes
- Serious comorbidity or poor medical conditions
- Pregnancy or Lactating woman
- Woman in child bearing age who refuses contraception
- Motor or sensory peripheral neuropathy ≥ Grade 1
- Other malignancy except cured basal cell carcinoma or uterine cervical carcinoma in situ
Recruitment

After 156 patients were randomized, from 2011 August to 2013 December, study team closed enrollment because of approval and use of maintenance pemetrexed treatment.
CONSORT Diagram

Randomized
n=156

Pemetrexed cisplatin
n=80

Withdraw consent
N=3

ITT*, Safety (n=77)
RE** (n=66)

Docetaxel cisplatin
n=76

Withdraw consent
N=4

ITT*, Safety (n=72)
RE** (n=64)

*ITT; intention to treat, **RE; response evaluable
Table 1. Comparison of characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed/Cisplatin (n=77)</th>
<th>Docetaxel/Cisplatin (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean(SD)</td>
<td>63.0 ± 8.9</td>
<td>63.8 ± 9.8</td>
</tr>
<tr>
<td>Sex</td>
<td>53/24</td>
<td>50/22</td>
</tr>
<tr>
<td>ECOG PS (0/1/2)</td>
<td>14/55/8</td>
<td>17/48/7</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.1 ± 3.45</td>
<td>22.6 ± 2.68</td>
</tr>
<tr>
<td>Histology ADC/LCC/NSCLC</td>
<td>75/0/2</td>
<td>69/1/2</td>
</tr>
<tr>
<td>Stage (IIIB/IV)</td>
<td>5/72</td>
<td>3/69</td>
</tr>
</tbody>
</table>
Table 2. Comparison of treatment

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed/Cisplatin (n=77)</th>
<th>Docetaxel/Cisplatin (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles (1/2/3/4/6)</td>
<td>7/16/2/49/3</td>
<td>11/14/1/45/1</td>
</tr>
<tr>
<td>Cycles mean(range)</td>
<td>3.4 (1-6)</td>
<td>3.2 (1-6)</td>
</tr>
<tr>
<td>Total number of Cycles</td>
<td>259</td>
<td>228</td>
</tr>
<tr>
<td>Cycles delayed</td>
<td>17 (6.7%)</td>
<td>18 (7.9%)</td>
</tr>
<tr>
<td>Doses reduced</td>
<td>16 (6.3%)</td>
<td>21 (9.3%)</td>
</tr>
<tr>
<td>Relative dose-intensity (%)</td>
<td>97.6 ± 5.7</td>
<td>96.2 ± 6.9</td>
</tr>
</tbody>
</table>
Table 3. Comparison of adverse events.

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed/Cisplatin (n=77)</th>
<th>Docetaxel/Cisplatin (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia grade 3/4</td>
<td>1 (1.3%)</td>
<td>10 (13.9%) **</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>1 (1.3%)</td>
<td>8 (11.1%) *</td>
</tr>
<tr>
<td>Anemia grade 1/2</td>
<td>1 (1.3%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>AST/ALT increased gr 1/2</td>
<td>0</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>1 (1.3%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Total number of SAE</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>Number of cases with SAE</td>
<td>17 (22.1%)</td>
<td>29 (40.3%) *</td>
</tr>
<tr>
<td>Fatal SAE</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01
Data survey in progress
**Pemetrexed Cisplatin**

- **Response rate (%)**
  - **ITT**: 24 / 33 / 10 / 10 (PR / SD / PD / NE)
  - **ITT**: 31.2%
  - **RE**: 35.8%

**Docetaxel Cisplatin**

- **Response rate (%)**
  - **ITT**: 24 / 25 / 15 / 8 (PR / SD / PD / NE)
  - **ITT**: 33.3%
  - **RE**: 38.7%

*ITT: intention to treat, **RE: response evaluable*
Progression Free Survival

- **Pem Cis:** 4.7 m (4.4-5.1)
- **Doc Cis:** 4.6 m (3.7-5.6)

Log rank p > 0.05
HR=1.016 (0.737~1.400)

c.f. Median PFS of Pem Cis
6.4 m in east Asian
- JTO 5(5), 2010
5.3 m in all ethnic group.
Efficacy & PFS by TS expression in Pem-Cis arm

<table>
<thead>
<tr>
<th>DAKO clone M3614</th>
<th>Thymidylate Synthase Low expressed</th>
<th>Thymidylate Synthase High expressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease control (PR+SD)</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Progression Free Survival

- **TS Low:** 5.7 m (2.8-8.6)
- **TS High:** 1.3 m (0-7.5)

P = 0.06

P = 0.19
Overall Survival

Pem Cis: 19.7 (10.8-28.6)
Doc Cis: 28.0 (7.5-48.5)

c.f. Median OS of Pem Cis
21.2 m in east Asian
- JTO 5(5), 2010
11.0 m in all ethnic group.
Table 4. Treatment beyond First line study*.

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed/Cisplatin (n=77)</th>
<th>Docetaxel/Cisplatin (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>18 (23.4%)</td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td></td>
<td>18 (25.0%)</td>
</tr>
<tr>
<td>EGFR-TKI</td>
<td>45 (58.4%)</td>
<td>33 (45.8%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>11 (14.3%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Other chemotherapy</td>
<td>4 (5.2%)</td>
<td>4 (5.6%)</td>
</tr>
</tbody>
</table>

* Data survey in progress
Table 5. Comparison of Pem-Cis data in prior studies

<table>
<thead>
<tr>
<th></th>
<th>All ethnicity(^1)</th>
<th>East Asian(^2)</th>
<th>Pem-Carbo(^3)</th>
<th>Paramount(^4)</th>
<th>Author’s trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>862</td>
<td>67</td>
<td>128</td>
<td>359</td>
<td>77</td>
</tr>
<tr>
<td>Non-Squamous</td>
<td>71.7%</td>
<td>70.1%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Age (median)</td>
<td>61.1</td>
<td>61.7</td>
<td>60.1</td>
<td>61</td>
<td>64.4</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>29.8%</td>
<td>31.3%</td>
<td>42</td>
<td>44%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>76.2%</td>
<td>74.6%</td>
<td>84%</td>
<td>91%</td>
<td>93.5%</td>
</tr>
<tr>
<td>EGFR-TKI</td>
<td>24.9%</td>
<td>56.7%</td>
<td>Not reported</td>
<td>41.4%</td>
<td>58.4%</td>
</tr>
<tr>
<td>Cycles (median)</td>
<td>5</td>
<td>5-6</td>
<td>5-6</td>
<td>4+maintenance</td>
<td>3.57</td>
</tr>
<tr>
<td>Response rate</td>
<td>32.0%(^\S)</td>
<td>46.5%(^\S)</td>
<td>34.0</td>
<td>30%</td>
<td>36%</td>
</tr>
<tr>
<td>PFS</td>
<td>5.3m(^\S)</td>
<td>6.4m(^\S)</td>
<td>5.8m</td>
<td>6.9m</td>
<td>4.7m</td>
</tr>
<tr>
<td>OS</td>
<td>11.0m(^\S)</td>
<td>21.2m(^\S)</td>
<td>14.9m</td>
<td>16.9m</td>
<td>19.7m (premature)</td>
</tr>
</tbody>
</table>

Conclusion

• In Non-Squamous NSCLC without driver mutations, Doc-Cis showed similar PFS and response rate, compared to Pem-Cis.

• More frequent adverse events and higher toxicities were observed in Doc-Cis arm.

• Numerically shorter PFS of both arms in this trial suggest that maintenance treatment should be considered unless disease progression is noted.
Acknowledgements

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  – Sanofi-Aventis Korea Ltd.