1234PD:
Randomized Phase III Trial of S-1 plus Cisplatin versus Docetaxel plus Cisplatin for Advanced Non-Small-Cell Lung Cancer (TCOG0701)
Hiroshi Sakai

1234PD:
PARAMOUNT: Descriptive subgroup analyses of final Overall Survival (OS) for the phase III Study of Maintenance Pemetrexed versus placebo (plb) following induction with pem plus cisplatin (cis) for advanced nonsquamous (ns-NSCLC)
Martin Reck

1236PD:
Tumour biomarker and plasma time course data from ABIGAIL, a phase II study of 1st-line bevacizumab + chemotherapy in advanced non-squamous non-small-cell lung cancer (ns-NSCLC)
Martin Reck
Randomized Phase III Trial of S-1 plus Cisplatin versus Docetaxel plus Cisplatin for Advanced Non-Small-Cell Lung Cancer (TCOG0701)

- CATS (Cisplatin And TS-1) TRIAL -

Hiroshi Sakai, Akihiko Gemma, Kaoru Kubota, Makoto Nishio, Hiroaki Okamoto, Akira Inoue, Hiroshi Isobe, Kunihiko Kobayashi, Masahiro Takeuchi, Shoji Kudoh

TCOG CATS TRIAL Study Group
CATS TRIAL (Cisplatin And TS-1 TRIAL)  
Treatment Schema

- Advanced NSCLC
- PS 0 or 1
- 20-74 years
- No prior chemotherapy

Control arm (DP) n=305
Docetaxel: 60mg/m² d1
Cisplatin: 80mg/m² d1
repeated every 3-4 weeks

Experimental arm (SP) n=303
S-1: 40-60mg* /body b.i.d d1-21
Cisplatin: 60mg/m² d8
repeated every 4-5 weeks

*According to body surface area
- BSA < 1.25 m² 80 mg/day
- 1.25=<BSA <1.5 100 mg/day
- BSA >=1.5 120 mg/day

Randomized

- Stratified by
  Gender (Male/Female)
  Stage (IIIB/IV/postoperative)
  histology (Adeno/Non-adeno)

- Follow-up : Jan/2009 - Jun/2011
- Enrolled : N=608

- Enrolled : N=608
Overall survival

<table>
<thead>
<tr>
<th></th>
<th>SP (n=301)</th>
<th>DP (n=295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (M)</td>
<td>17.1 months</td>
<td>16.1 months</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(13.7-20.3)</td>
<td>(14.0-18.5)</td>
</tr>
<tr>
<td>HR (96.4% CI)</td>
<td>1.013 (0.837-1.227)</td>
<td></td>
</tr>
<tr>
<td>N Events</td>
<td>244</td>
<td>236</td>
</tr>
</tbody>
</table>

**Median Overall Survival by Histology**

<table>
<thead>
<tr>
<th></th>
<th>Non-squamous</th>
<th>Squamous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP (n=251)</td>
<td>DP (n=247)</td>
</tr>
<tr>
<td>Median OS (M)</td>
<td>17.4</td>
<td>19.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(14.6-20.7)</td>
<td>(14.6-21.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.973 (0.797-1.187)</td>
<td>1.239 (0.819-1.874)</td>
</tr>
</tbody>
</table>
Patients responded to EORTC QLQ-C30 3 times:
1. before each treatment
2. 1 week after the first dose of cisplatin
3. at the end of the second course.

A higher score of LC-13 represents a worse condition in lung cancer-associated symptoms, treatment-related side effects and pain.
Conclusions

• S-1 plus cisplatin was demonstrated to be non-inferior to docetaxel plus cisplatin in terms of OS as assessed by predefined criteria.

• No difference in PFS and RR were observed.

• S-1 plus cisplatin was better tolerated than docetaxel plus cisplatin, especially in terms of febrile neutropenia and QOL.

• S-1 plus cisplatin is a new standard first-line chemotherapeutic regimen for advanced NSCLC.
S-1 in metabolism of 5-FU

(J Thorac Oncol. 2011;6: 1400–1406)
Conclusions

• Phase II trials in Japan have shown promising efficacy (RR 33-47%; OS 11-16 month)
• Some testing (no PhIII) have been done in US
• No clinical trials have been performed in Europe
Conclusions

• Chemotherapy regimen different from earlier trials
  – Okamoto 2010: S1+Carbo (AUC=5) vs Carbo (AUC=6 and paclitaxel 200 mg/m²)

• Thus not a standard CT control-arm
Conclusions

• S-1 alone, or in combination with cisplatin, appears to be active in NSCLC
• The oral formulation is a big advantage
• This dublet does not appear to be superior to other platinumbased dublet regimens
• Further clinical trials are warranted in Europe to compare with standard dublets (Cis/Gem; Carbo/Vino etc)
Conclusions

• No testing for oncogene drivers were done
  – EGFR M; EML4/ALK etc.
PARAMOUNT: Descriptive subgroup analyses of final overall survival (OS) for the Phase III Study of Maintenance Pemetrexed (PEM) versus Placebo (PLB) Following Induction treatment for advanced Nonsquamous (ns) NSCLC

PARAMOUNT: Study Design

- Randomized, placebo-controlled, double-blind phase III study
- Pemetrexed 500 mg/m²; Cisplatin 75 mg/m²
- Folic acid and vitamin B₁₂ administered to both arms

**Induction Therapy**
- 4 cycles, q21d

**Continuation Maintenance Therapy**
- q21d until PD

CR/PR/SD per RECIST

**Randomized, placebo-controlled, double-blind phase III study**

- Pemetrexed 500 mg/m²; Cisplatin 75 mg/m²
- Folic acid and vitamin B₁₂ administered to both arms

**Previously untreated**
- PS 0/1
- Stage IIIB-IV NS-NSCLC

**Pemetrexed + Cisplatin**

- CR/PR/SD per RECIST

**Pemetrexed + BSC**

**Placebo + BSC**

**Stratified for:**
- PS (0 vs 1)
- Disease stage (IIIB vs IV) prior to induction
- Response to induction (CR/PR vs SD)
## PARAMOUNT: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed (N=359)</th>
<th>Placebo (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age, yrs</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>&lt; 65 yrs, %</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>Male, %</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Smoker, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever Smoker</td>
<td>76</td>
<td>80</td>
</tr>
<tr>
<td>Never Smoker</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>2/3*</td>
<td>0.3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Protocol violations.*
PARAMOUNT: Final Patient Disposition

1022 Patients Screened

83 Patients Failed Screening

939 Patients Enrolled

539 Patients Randomized (2:1 Randomization)

548 Patients Eligible for Maint
8 Discontinued Pt Decision
1 Discontinued Phys Decision

Pemetrexed Arm N=359
- 256 (71%) Pts with events at data cut off
- 350 (97%) Pts discontinued treatment

Placebo Arm N=180
- 141 (78%) Pts with events at data cut off
- 178 (99%) Pts discontinued treatment

400 Patients Not Randomized
- 217 Progressive Disease
- 62 Adverse Event
- 56 Death
  - 29 Study Disease
  - 15 AE
  - 11 Drug-Related AE
  - 1 Procedure-Related AE
- 65 Other Reasons

269 Patients Enrolled

1522 Patients Screened

439 Patients Enrolled

539 Patients Randomized (2:1 Randomization)

548 Patients Eligible for Maint
8 Discontinued Pt Decision
1 Discontinued Phys Decision

Pemetrexed Arm N=359
- 256 (71%) Pts with events at data cut off
- 350 (97%) Pts discontinued treatment

Placebo Arm N=180
- 141 (78%) Pts with events at data cut off
- 178 (99%) Pts discontinued treatment
PARAMOUNT: Final OS from Randomization

<table>
<thead>
<tr>
<th>Time from Randomization (Months)</th>
<th>Pem</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>21</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>27</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>30</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>33</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>36</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS Median (mo) (95% CI)</th>
<th>Pem</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pem</td>
<td>13.9</td>
<td>11.0</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(12.8-16.0)</td>
<td>(10.0-12.5)</td>
</tr>
<tr>
<td>Censoring (%)</td>
<td>28.7</td>
<td>21.7</td>
</tr>
<tr>
<td>Survival Rate (%) (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>58 (53-63)</td>
<td>45 (38-53)</td>
</tr>
<tr>
<td>2-year</td>
<td>32 (27-37)</td>
<td>21 (15-28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Pem + BSC</th>
<th>Placebo + BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pem</td>
<td>359</td>
<td>180</td>
</tr>
<tr>
<td>BSC</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>OS Median (mo) (95% CI)</td>
<td>13.9 (12.8-16.0)</td>
<td>11.0 (10.0-12.5)</td>
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<td>58 (53-63)</td>
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<tr>
<td>2-year Survival Rate (%) (95% CI)</td>
<td>32 (27-37)</td>
<td>21 (15-28)</td>
</tr>
</tbody>
</table>
The survival results were internally consistent; benefit was seen across all subgroups.
1235PD: Conclusions

- This poster summarizes baseline characteristics for pts on the pem arm surviving for 6-24 months after randomization.

- Characteristics of pts surviving for longer periods were comparable to those of pts surviving shorter periods.

- This suggests OS benefit for all subgroups of pts on maintenance therapy.

- PS was the only baseline characteristic associated with improved OS.
In PARAMOUNT, the OS benefit was seen across all subgroups.

Other than PS, no baseline or clinical parameter clearly identifies a subgroup more likely to benefit.

Maintenance treatment decisions should be made on an individual basis.
Commentary

Maintenance Therapy and Advanced Non–Small-Cell Lung Cancer

A Skeptic’s View

Martin J. Edelman, MD,* Thierry Le Chevalier, MD,† and Jean-Charles Soria, MD, PhD†
The Fidias trial specifically reported the outcomes of patients in the pcb arm who received docetaxel - and showed no difference.

No other study has reported the outcomes for control patients who either crossed-over to the "study agent" or to another acceptable drug.
An unacceptable high number of patients failed to receive any therapy. Up to 60% of patients got treatment. This is not the overall NSCLC population, but patients that were stable or responding after CT. In such a group of pts around 80% receive 2nd line therapy.
No data has been provided regarding why patients on the control arm did not receive additional therapy.

This issue is critical
Optimal design of a switch-maintenance trial

(J Thorac Oncol. 2012;7: 1331–1336)
Conclusions

• No useful patients selection was seen in this analysis
• There is an urgent need for biomarker(s) to select patients for maintenance therapy
• CT every 21 d is not for all patients
• No QoL reported in PARAMOUNT
• No report on oncogene drivers (EGFR M; EML4/ALK etc)
Tumour biomarker and plasma time course data from ABIGAIL, a phase II study of 1st-line bevacizumab + chemotherapy in advanced non-squamous non-small-cell lung cancer (ns-NSCLC)

Martin Reck,¹ Vera Gorbunova,² Erzsebet Juhasz,³ Barna Szima,⁴ Sergey Orlov,⁵ Chung-Jen Yu,⁶ Celine Pallaud,⁷ Stefan J Scherer,⁷ Venice Archer,⁸ Tony Mok⁹

¹Department of Thoracic Oncology, Hospital Grosshansdorf, Germany; ²Russian Research Oncology Center n.a. N.N. Blokhin of the Russian Academy of Medical Sciences, Russia; ³Országos Korányi TBC és Pulmonológiai Intézet, Hungary; ⁴Markusovszky Hospital Oncoradiology, Hungary; ⁵St Petersburg State Medical University, St Petersburg, Russia; ⁶National Taiwan University Hospital, Taiwan; ⁷F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁸Roche Products Ltd, Welwyn Garden City, UK; ⁹State Key Laboratory of Southern China, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China
**BO21015 (ABIGAIL) study design and endpoints**

- **Primary endpoint:** explore correlation between candidate biomarkers and ORR to chemotherapy + bevacizumab
- **Secondary endpoint:** PFS; ORR; DCR; duration of response; OS and safety

**Key exploratory endpoints:**
changes in candidate biomarkers across time, tumour biomarkers, correlation of tumour volume changes

**Previously untreated, stage IIIB, IV or recurrent non-squamous NSCLC**
(n=300)
Stratified by stage, gender, PS, chemotherapy regimen

**Bevacizumab 7.5mg/kg q3w**
+ up to six 21-day cycles of carboplatin/gemcitabine* or carboplatin/paclitaxel* (n=150)

**Bevacizumab 15mg/kg q3w**
+ up to six 21-day cycles of carboplatin/gemcitabine* or carboplatin/paclitaxel* (n=150)

**Bevacizumab 7.5mg/kg until progression**
PD

**Bevacizumab 15mg/kg until progression**
PD
No cross-over permitted

*Chemotherapy regimen was not randomly allocated but was chosen by the Investigator

**PS = performance status; PD = progressive disease; ORR = overall response rate; DCR = disease control rate**
Biomarker analyses methodology

Biomarker analysis

- Plasma biomarkers VEGFA, VEGFR-1, VEGFR-2, bFGF, E-selectin, PIGF and ICAM were assessed by IMPACT assay.
- The plasma biomarker VEGFA was measured at baseline only, as the assay was unable to reliably measure VEGFA during bevacizumab treatment.
- Formalin-fixed paraffin-embedded tumour samples were analysed by IHC.
  - VEGFR-1, MVD, VEGFA, VEGFR-2 and NRP1.
- Median biomarker levels were calculated and used to define high (>median) versus low (≤median) biomarker levels for each candidate marker.

Statistical analysis

- Correlations and interactions were assessed by Cox/logistic and multiple Cox/logistic regression, respectively.

Data presented

- Correlation of plasma VEGFA at baseline with OS.
- Change in plasma biomarker levels from baseline to disease progression.
- Correlation of tumour VEGFR-1 with OS.
- Correlation between tumour and plasma biomarkers.

VEGFA = vascular endothelial growth factor-A; VEGFR-1 = vascular endothelial growth factor receptor-1; VEGFR-2 = vascular endothelial growth factor receptor-2; bFGF = basic fibroblast growth factor; ICAM = intracellular adhesion molecule 1; PIGF = placental growth factor; MVD = microvessel density; NRP1 = neuropilin 1; IHC = immunohistochemistry.
Collection of tumour/plasma samples for biomarker analysis

Plasma samples collected at end of every second cycle

Baseline plasma sample
End cycle 2/ before cycle 3 administration
Plasma sample at completion of combination therapy
Plasma sample at disease progression

Screening → Treatment period → PD

Monotherapy period

End cycle 4/ before cycle 5 administration

All efforts made to provide tumour samples if available

Collection of tumour/plasma samples for biomarker analysis

- Biomarker evaluable population (BEP)
  - 287 patients consented to provide plasma samples (95%)
  - 94 archival tumour samples (31%) could be analysed fully out of 169 consented patients
Scheduling of tumour assessments

Assessments carried out at the end of every second cycle

End of cycle 2/ before cycle 3 administration

End of cycle 4/ before cycle 5 administration

End cycle 6

Monotherapy period

Assessments carried out at the end of every second cycle until disease progression

Screening

Treatment period

[Cycles 1 – 6]

Baseline HRCT scan carried out within 14 days of starting treatment

End of cycle 6

[Cycle 7 onwards]

Note: scan data was also used to reconstruct the 3-D images for the volumetric part of the study;
HRCT = high-resolution computed tomography
The OS results were consistent with the results previously reported for PFS in Mok, ESMO 2012.
No significant changes in plasma levels were observed at any time during the course of treatment for tested markers
Tumour biomarker analyses

- All tumour sample analyses were carried out using archival material.
- No significant correlations were observed between tumour markers investigated and BOR, PFS or OS.
- Interaction tests for OS highlighted one significant interaction:
  - High tumour levels of VEGFR-1 were significantly associated with shorter OS ($p=0.0371$).
- Only one correlation between tumour and plasma biomarkers was detected:
  - Tumour VEGFR-1 expression and baseline plasma VEGFA ($p=0.025$).
Conclusions

• In these exploratory ABIGAIL biomarker analyses:
  - low baseline plasma VEGFA was associated with longer OS
  - there was no significant change in any biomarker level over the course of disease progression
  - a correlation was noted between high tumour VEGFR-1 levels and poor OS when adjusted for multiple testing
  - however, without adjustment for multiple testing, no investigated tumour biomarker was found to be significantly correlated with BOR, PFS or OS

• Additional exploratory analyses are ongoing to better understand the ABIGAIL dataset and the complex biology of angiogenesis
  - further investigations are required to understand the potential prognostic and/or predictive value of these findings

My Conclusions

• Dissapointing that no marker was usefull
  - We urgently need predictive markers of anti-angiogenic therapy

• Many design issues to be learned from the ABIGAIL trial
  - Well-designed trial
  - Sampling of blood
  - Evaluation intervals

• Only 31% tumor samples suitable for analyses is not good enough
  - We need to be better in ensuring these very important samples
  - And/or we need to be better to use smaller samples
Overall conclusions

• PhIII trials need to be selected or stratified for oncogene drivers (EGFR M; EML4/ALK etc)
  – Unselected PhIII trials is a waste of patients
• Selection of patients to maintenance is warranted
  – Pem, Bev or others
• QoL measurements are required in maintenance trials
• Collection of biopsies, blood samples and re-biopsies are crucial for our understanding of tumor biology/pathology
  – ”The tissue is the issue” --- but the blood might be enough