Targeted Therapies in Non Small-Cell Lung Cancer

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Medical Oncology Centre
Gleneagles Cancer Centre
Singapore
Outline of Presentation

- Lung cancer – the Disease
- Brief overview of molecular cancer biology in particular EGFR and angiogenesis
- Summary of early clinical data on anti-EGFR therapy
- Review of key Avastin™ and Tarceva™ Phase III data and perspective
- New directions in targeted therapy for NSCLC and 2007 update
Van Gogh’s Painting of Lung Cancer
Smoking and Lung Cancer in Asia
Revolutions in Cancer

Surgical Oncology
- Organ sparing surgery
- Laparoscopic surgery
- Robotic surgery

Diagnostic Tools
- CT, MRI, PET-CT scans
- Molecular pathology
- Biomarkers of cancer

Radiation Oncology
- Linear accelerator
- IMRT
- IGRT
- Tomo-RT

Medical Oncology
- New cytotoxic and hormonal drugs
- Molecular targeted drugs
- Stem cell transplantation
- New supporting drugs
The Challenge of NSCLC

- Lung cancer is a devastating disease
  - one of the most common cancers globally
  - associated with a high mortality rate
- NSCLC comprises 80% of lung cancers
- Most patients present with advanced disease:
  - ~20% stage IIIA/IIIB (poor prognosis)
  - >50% stage IV disease (limited treatment options)
- Such patients may be unable to tolerate conventional treatments

American Cancer Society: Cancer facts and figures. 1999, Atlanta GA.
Facts about Advanced NSCLC

- Newly diagnosed advanced NSCLC have median survival (MS) of 8 to 10 months and 1-year overall survival (OS) of 30 to 35% when treated with standard chemotherapy.
- Patients with refractory NSCLC face a MS of only 4 to 5 months and 1-year OS of 11% without further treatment.
- For those who can tolerate additional treatment, second-line chemotherapy yields a MS of 7 months and 1-year OS of 30%.
Management of lung cancer is getting more complex – increasing use of multidisciplinary approaches, depending on the stage of the disease at the time of diagnosis.

- Doublet chemotherapy improves survival and QoL in patients with advanced disease (stage IIIB with pleural effusion and stage IV)
  - Efficacy of current regimens has reached its limits

- Significant toxicity of many current treatments

- Monoclonal antibodies and targeted agents in combination with chemotherapy are being evaluated
  - improved response
  - acceptable toxicity
A therapeutic plateau has been reached for chemotherapy

## Non Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>The East</th>
<th>The West</th>
</tr>
</thead>
<tbody>
<tr>
<td>- % Smoker</td>
<td>50 – 60%</td>
<td>80 – 90%</td>
</tr>
<tr>
<td>- % smoker in female patients</td>
<td>&lt; 10%</td>
<td>80%</td>
</tr>
<tr>
<td>- % objective response to chemo</td>
<td>40 – 70%</td>
<td>20 – 40%</td>
</tr>
<tr>
<td>- Median survival for patients with Advanced disease (IIIB &amp; IV)</td>
<td>12 – 24m</td>
<td>8 – 12m</td>
</tr>
<tr>
<td>- Response rate to EGFR TK I in unselected patients</td>
<td>20 – 40%</td>
<td>&lt; 10%</td>
</tr>
</tbody>
</table>
Novel approaches are required

Invasion

Angiogenesis/vasculature

Signal transduction

Cell cycle

Metastasis

Apoptosis
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HER/ErbB family of receptors
The HER/ErbB family of receptors and ligands

Ligands
- EGF
- TGFα
- Amphiregulin
- β-cellulin
- HB-EGF
- Epiregulin
- NRG2
- NRG3
- Heregulins
- β-cellulin

Tyrosine kinase domain
- ErbB-1 (Her1)
- ErbB-2 (Her2/neu)
- ErbB-3 (Her3)
- ErbB-4 (Her4)

Cysteine-rich domains
- 100
- 100
- 100
- 100

C-terminus
- 82
- 33
- 24
- 28

Woodburn J. Pharmacol Ther 1999;82:241–250
Effects of HER1/EGFR signal transduction in tumor cells

DNA
- myc
- cyclin D1
- Jun
- Fos
- Myc

Gene transcription
- Cell cycle progression

proliferation/maturation
chemotherapy/radiotherapy resistance
survival/anti-apoptosis
angiogenesis
metastasis

Effects of HER1/EGFR signal transduction in tumor cells

Tumours with HER1/EGFR dysregulation

Woodburn JR. Pharmacol Ther 1999;82:241–50
EGFR expression in human lung cancer

<table>
<thead>
<tr>
<th></th>
<th>Rusch 1993</th>
<th>Rusch 1997</th>
<th>Fontanini 1998</th>
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<tbody>
<tr>
<td>EGFR expression</td>
<td>93%</td>
<td>-</td>
<td>81%</td>
</tr>
<tr>
<td>TGFα expression</td>
<td>88%</td>
<td>-</td>
<td>99%</td>
</tr>
<tr>
<td>EGF expression</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EGFR overexpression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>45%</td>
<td>70%</td>
<td>49%</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>68%</td>
<td>92%</td>
<td>57%</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>36%</td>
<td>58%</td>
<td>38%</td>
</tr>
</tbody>
</table>
VEGF & Angiogenesis
VEGF & Angiogenesis

- VEGF = Vascular Endothelial Growth Factor
- Angiogenesis = formation of new blood vessels
- VEGF is the central mediator of angiogenesis
- Regulates angiogenesis
- Promotes survival of immature vasculature
VEGF: A Central Mediator of Angiogenesis

Environmental factors
(Hypoxia, pH)

Growth factors
Hormones
(EGF, bFGF, PDGF, IGF-1, IL-1α, IL-6, estrogen)

Genes involved in tumorigenesis
(p53, p73, src, ras, vHL, Her2/neu, EGFR bcr-Abl)

Binding and activation of VEGF receptor

Endothelial cell activation

Survival  Proliferation  Migration

ANGIOGENESIS
Angiogenesis is involved throughout tumour formation, growth and metastasis

Angiogenesis = formation of new blood vessels
Plays a role in tumour progression

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HER1/EGFR as a new target for anticancer therapy
**Tarceva: mode of antitumour activity**

Mechanism of action: inhibit TK autophosphorylation by competing with ATP for the active site of the intracellular TK domain

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40 year old Chinese man. Non smoker
Advanced lung cancer

25 July 2005
Erlotinib (Tarceva™) 150mg tablet/day

23 Sept 2005
Outline of Presentation

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Overview of oral TKI - EGFR

- **Four 1st line randomized trials:**
  - Chemotherapy +/- gefitinib v placebo
  - Chemotherapy +/- erlotinib v placebo
  The addition of an oral TKI to standard chemotherapy **DOES NOT** improve survival.

- **Two 2nd/3rd line randomized trials**
  - Gefitinib v placebo (ISEL: HR 0.89, p =0.087)
  - Improved OS (HR 0.70; p <0.001) and symptoms/quality of life.
  - Presence of rash predicts for efficacy
Erlotinib in Previously Treated Non–Small-Cell Lung Cancer

Frances A. Shepherd, M.D., José Rodrigues Pereira, M.D., Tudor Ciuleanu, M.D., Eng Huat Tan, M.D., Vera Hirsh, M.D., Sumitro Thongprasert, M.D., Daniel Campos, M.D., Savitree Maoleekoonpiroj, M.D., Michael Smylie, M.B., Ch.B., Renato Martins, M.D., Maximiliano van Kooten, M.D., Mircea Dediu, M.D., Brian Findlay, M.D., Dongsheng Tu, Ph.D., Dianne Johnston, Andrea Bezjak, M.D., Gary Clark, Ph.D., Pedro Santabárbara, M.D., Ph.D., and Lesley Seymour, M.D., Ph.D., for the National Cancer Institute of Canada Clinical Trials Group
BR.21 schema

Stratified by
Centre
PS (0/1 vs 2/3)
Response prior Rx (CR/PR:SD:PD)
Prior regimens (1 vs 2)
Prior platinum (Yes vs no) N = 731

Tarceva™
150mg daily
N = 488

Placebo
‘150mg’ daily
N = 243

PS = performance status; CR = complete response
PR = partial response SD = stable disease; PD = progressive disease; *2:1 randomisation
Study endpoints

- **Primary**
  - overall survival

- **Secondary**
  - progression-free survival (PFS)
  - time to deterioration of cough, dyspnea, pain as per EORTC QLQ-C30 + QLQ-LC13
  - response rates, duration
  - toxicity and tolerability
  - tissue HER1/EGFR versus outcome and safety

HER/EGFR = human epidermal growth factor receptor
43 year old Female Chinese, Non-Smoker

14 Oct 2005: before Tarceva

5 Dec 2005: 2 months after Tarceva
5 Dec 2002: 2 months after Tarceva

14 Oct 2002: before Tarceva

26 Aug 2006: 10 months of Tarceva
BR.21 : Progression-free survival

HR=0.61, p<0.001*

Tarceva (n=488)  
Placebo (n=243)

<table>
<thead>
<tr>
<th>Median survival (weeks)</th>
<th>Tarceva</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.7</td>
<td>8.0</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>6 months PFS (%)</th>
<th>Tarceva</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

HR=0.61, p<0.001*  


*HR and p (log-rank test) adjusted for stratification factors at randomisation and HER1/EGFR status
Overall survival: Tarceva significantly prolongs survival in relapsed advanced NSCLC

Tarceva (n=488)
Placebo (n=243)

Median survival (months) 6.7 4.7
1-year survival (%) 31 21

HR=0.73, p<0.001*


*HR and p (log-rank test) adjusted for stratification factors at randomisation and EGFR status
## BR.21 adverse events (%)

<table>
<thead>
<tr>
<th></th>
<th>Tarceva™ (n=485)</th>
<th>Placebo (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Grade 3, 4</td>
</tr>
<tr>
<td>Rash</td>
<td>75</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td>Ocular (all)</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>52</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>24</td>
<td>4</td>
</tr>
</tbody>
</table>
Oral EGFRI toxicity: Acneiform skin rash
BR.21: survival according to EGFR gene copy number (FISH)

**EGFR FISH negative**
- **Tarceva (n=45)**
- **Placebo (n=24)**

HR=0.85 (0.48–1.51)
p=0.59*

**EGFR FISH positive**
- **Tarceva (n=32)**
- **Placebo (n=24)**

HR=0.44 (0.23–0.82)
p=0.008*

Treatment x FISH status: p=0.10 (not significant) Cox regression analysis

*Log-rank test

Survival for females and males – BR.21

Females

Placebo (n=83)
Median 6.2mths

Tarceva™ (n=173)
Median 8.4 mths

HR = 0.80

Males

Placebo (n=160)
Median 4.5mths

Tarceva™ (n=315)
Median 5.7mths

Females and males benefit equally from Tarceva™
Survival for adenocarcinomas and squamous-cell carcinoma - BR.21

Adenocarcinomas

Placebo (n=119)
Median 5.4mths

Tarceva™ (n=246)
Median 7.8mths

HR=0.71 (95% CI 0.56 to 0.92)

Squamous-cell carcinoma

Placebo (n=78)
Median 3.6mths

Tarceva™ (n=144)
Median 5.6mths

HR=0.67 (95% CI 0.50 to 0.90)

Patients with adenocarcinoma and squamous cell carcinoma benefit equally to Tarceva™
**BR.21: summary of significant clinical predictors of response**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Tarceva Patients (%) (n=427)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Male</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>18.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Other</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td><strong>Ever smoked</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13.0</td>
<td></td>
</tr>
</tbody>
</table>

*Significance between subgroups*
Overall summary of Tarceva in NSCLC

- Tarceva™ therapy significantly
  - prolonged survival
  - delayed disease progression
  - delayed worsening of lung cancer-related symptoms

- Efficacy was robust and homogeneous across a wide range of patient subsets

- In multivariate analysis, adenocarcinoma (p=0.01), never-smoking (p<0.001) and EGFR expression (IHC) (p = 0.03) are associated with response; BUT, survival not influenced by EGFR expression, copy or mutation

- Tarceva™ was well tolerated
  - rash, diarrhoea most common events, generally mild or moderate

- This is the first placebo-controlled trial to demonstrate that an HER1/EGFR inhibitor prolongs survival
Avastin (Bevacizumab)

- Recombinant humanised monoclonal antibody (Mab)
- 93% human & 7% murine in origin
- Bind to human VEGF specifically
- Recognised all isoforms of VEGF
Effects of anti-VEGF therapy

EARLY EFFECTS

1. Regression of existing tumour microvasculature\textsuperscript{1–8}
2. Normalisation of remaining tumour vasculature\textsuperscript{5–9}

CONTINUED EFFECTS

3. Inhibition of new tumour vasculature\textsuperscript{1,2,8,10,11}

\textsuperscript{5}Jain RK. Nat Med 2001;7:987–9; \textsuperscript{6}Jain RK. Science 2005;307:58–62
A randomised phase III trial of paclitaxel plus carboplatin with or without bevacizumab in patients with advanced non-squamous non-small cell lung cancer: an Eastern Cooperative Oncology Group trial – E4599

Sandler AB, Gray R, Brahmer J, Dowlati A, Schiller J H, Perry MC, and Johnson DH

Vanderbilt-Ingram Cancer Center, Dana-Farber Cancer Center, Johns Hopkins University, Case-Western Reserve University Hospitals, University of Wisconsin, University of Missouri-Ellis Fischel Cancer Center

Phase III trial of bevacizumab in non-squamous NSCLC: ECOG 4599

Eligibility
Non-squamous NSCLC
No history of haemoptysis
No CNS metastases

Stratification variables
RT versus no RT
Stage IIIB or IV versus recurrent
Weight loss <5% versus >5%
Measurable versus non-measurable

(CP)
Paclitaxel 200mg/m²
carboplatin AUC = 6
(q3 weeks) x 6 cycles

(CP+A)
PC x 6 cycles
+ bevacizumab (Avastin)
(15mg/kg q3 weeks) to PD

No crossover to bevacizumab permitted

ECOG = Eastern Cooperative Oncology Group;
CNS = central nervous system; RT = radiotherapy

E4599 trial: improvement in PFS when Avastin is added to standard first-line therapy

HR=0.66 (0.57–0.77); p<0.001

E4599: improvement in overall survival when Avastin is added to standard first-line therapy

In this milestone trial, Avastin-based therapy extended median overall survival beyond 1 year

Survival (%)

<table>
<thead>
<tr>
<th></th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>44</td>
<td>15</td>
</tr>
<tr>
<td>CP + Avastin</td>
<td>51</td>
<td>23</td>
</tr>
</tbody>
</table>

HR=0.79 (0.67–0.92); p=0.003

Conclusions of Eastern Cooperative Oncology Group trial – E4599

- Bevacizumab improves survival when added to PC chemotherapy in patients with non-squamous NSCLC
- Bevacizumab also improves response rate and progression-free survival
- Bevacizumab is associated with a small increase in serious bleeding, including haemoptysis
- PCB is now the ECOG reference standard for the first-line treatment of advanced non-squamous cell NSCLC
- Future plans include
  - combination with chemotherapy and radiotherapy
  - combination with other targeted agents
  - neo-adjuvant and adjuvant settings
AVAiL – Avastin in Lung Cancer (B017704)

A randomised, double blind, phase III study of bevacizumab in combination with cisplatin and gemcitabine, versus placebo with cisplatin and gemcitabine in chemo-naïve patients with advanced or recurrent non-squamous NSCLC


PASCO 2007
**Study design**

- **Primary endpoint**
  - PFS
  - initially overall survival prior to protocol amendment

- **Secondary endpoint included**
  - overall survival; response rates; duration of response; safety

CG = cisplatin/gemcitabine
PFS: primary analysis (intent-to-treat) of Avastin 7.5mg/kg versus pooled placebo

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Placebo + CG</th>
<th>Avastin 7.5 mg/kg + CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(n=347)</td>
<td>(n=345)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>–</td>
<td>0.75</td>
</tr>
<tr>
<td>p value</td>
<td>–</td>
<td>0.0026</td>
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No. at risk

<table>
<thead>
<tr>
<th>Placebo + CG</th>
<th>Avastin 7.5 + CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>347</td>
<td>345</td>
</tr>
<tr>
<td>228</td>
<td>251</td>
</tr>
<tr>
<td>122</td>
<td>150</td>
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<tr>
<td>36</td>
<td>52</td>
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<tr>
<td>12</td>
<td>18</td>
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<tr>
<td>3</td>
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</table>
PFS: primary analysis (intent-to-treat) of Avastin 15mg/kg versus pooled placebo

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Placebo + CG (n=347)</th>
<th>Avastin 15 mg/kg + CG (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>–</td>
<td>0.82 (0.68, 0.98)</td>
</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>6</td>
<td></td>
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<td>9</td>
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<td>12</td>
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<td>18</td>
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No. at risk

<table>
<thead>
<tr>
<th>Placebo + CG</th>
<th>Avastin 7.5 + CG</th>
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<tbody>
<tr>
<td>347</td>
<td>351</td>
</tr>
<tr>
<td>228</td>
<td>238</td>
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<tr>
<td>122</td>
<td>148</td>
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<td>3</td>
<td>5</td>
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</table>
Prospective exploratory PFS analyses showed that the benefit was generally consistent across all subgroups studied.

<table>
<thead>
<tr>
<th></th>
<th>Placebo + CG (n=347)</th>
<th>Avastin 7.5mg/kg + CG (n=345)</th>
<th>Avastin 15mg/kg + CG (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (%)</td>
<td>78.6</td>
<td>88.5</td>
<td>80.7</td>
</tr>
<tr>
<td>6 months (%)</td>
<td>52.0</td>
<td>62.3</td>
<td>57.5</td>
</tr>
<tr>
<td>9 months (%)</td>
<td>19.2</td>
<td>28.5</td>
<td>25.3</td>
</tr>
<tr>
<td>12 months (%)</td>
<td>9.7</td>
<td>14.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>6.1</td>
<td>6.7</td>
<td>6.5</td>
</tr>
</tbody>
</table>
### Tumour Response and Response Duration

**Patient with Measurable Disease at Baseline**

|                      | Placebo + CG  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n = 347</td>
</tr>
<tr>
<td><strong>Response Rate %</strong></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>[4.6, 5.6]</td>
</tr>
</tbody>
</table>

|                      | Bevacizumab 7.5/kg + CG  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 345</td>
</tr>
<tr>
<td><strong>Response Rate %</strong></td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>[5.1, 7.0]</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

|                      | Bevacizumab 15/kg + CG  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 351</td>
</tr>
<tr>
<td><strong>Response Rate %</strong></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>[5.0, 6.6]</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.0017</td>
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|                      | **Duration of Response** | Placebo + CG  
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<tr>
<td></td>
<td>Median [95% CI]</td>
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<tr>
<td><strong>Duration of Response</strong></td>
<td>4.7 [4.6, 5.6]</td>
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</table>
|                      |                          | Bevacizumab 7.5/kg + CG  
|                      | Median [95% CI]          | n = 345        |
|                      | 6.1 [5.1, 7.0]          |
|                      |                          | Bevacizumab 15/kg + CG  
|                      | Median [95% CI]          | n = 351        |
|                      | 6.1 [5.0, 6.6]          |
Conclusions of AVAiL Trial

- AVAiL is the second phase III trial showing benefit from bevacizumab therapy in advanced NSCLC
- Similar benefit was seen in both bevacizumab doses
- CG in combination with bevacizumab (7.5mg/kg and 15mg/kg) was well tolerated with low rate of severe hemoptysis/pulmonary hemorrhage
- Overall survival data are pending
Conclusions of Avastin™ in NSCLC

- Avastin™ plus chemotherapy can achieve long-term disease control
- The combination is safe and well tolerated
- No major adverse events observed with prolonged Avastin™ treatment (> one year)
- Avastin™ did not increase chemotherapy-related toxicity in patients with NSCLC
Outline of Presentation

- Lung cancer – the Disease

- Brief overview of molecular cancer biology in particular EGFR and angiogenesis

- Summary of early clinical data on anti-EGFR therapy

- Review of key Avastin™ and Tarceva™ Phase III data and perspective

- New directions in targeted therapy for NSCLC and 2007 update
Tarceva™ and Avastin™: targeting the tumour and the vasculature

**Inhibitor**

**Mechanism**

**Tarceva™**
Inhibits tumour cell growth and blocks synthesis of angiogenic proteins (e.g. bFGF, VEGF, TGF-α) by tumour cells

**Avastin™**
Inhibits endothelial cells from responding to the angiogenic protein VEGF
Phase II study of Avastin™ with chemotherapy or Tarceva™ in advanced NSCLC

- Randomised, multicentre study
- Primary endpoint: safety and preliminary efficacy (PFS)
- Secondary endpoints: objective RR (+ duration); duration of survival

Avastin 15mg/kg every 3 weeks; Tarceva 150mg/day orally; docetaxel 75mg/m² and pemetrexed 500mg/m² every 3 weeks
PD = progressive disease

Phase II study of Avastin™ plus chemotherapy or Tarceva™ in advanced NSCLC: efficacy

**PFS**

- **Avastin + Tarceva**: Median 4.4 months, 6-month rate 33.6%
- **Avastin + CT**: Median 4.8 months, 6-month rate 30.5%
- **CT**: Median 3 months, 6-month rate 21.5%

**Overall survival**

- **Avastin + Tarceva**: Median 13.7 months, 1-year rate 57.1%
- **Avastin + CT**: Median 12.6 months, 1-year rate 53.6%
- **CT**: Median 8.6 months, 1-year rate 34.8%

Treatment options for advanced NSCLC (stage IIIB with pleural effusion/stage IV): addition of Avastin™

Suitable for chemotherapy?
- Yes
- No (PS 3–4, elderly)

Best supportive care

First line
- Platinum doublet + Avastin*
- Platinum doublet
- Single-agent chemotherapy (elderly/poor PS)

Second line
- Tarceva monotherapy or chemotherapy (docetaxel or pemetrexed)

Third line
- Tarceva monotherapy or best supportive care

Best supportive care

**How has NSCLC treatment changed in the 21st century?**

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<thead>
<tr>
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<th>1999</th>
<th>2007</th>
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<tbody>
<tr>
<td><strong>Adjuvant chemotherapy for early-stage</strong></td>
<td>Uncommon</td>
<td>Increasing</td>
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<tr>
<td><strong>First-line treatment for advanced</strong></td>
<td>Platinum-based doublets</td>
<td>Avastin™ + platinum-based doublet</td>
</tr>
<tr>
<td><strong>Second-line treatment for advanced</strong></td>
<td>BSC</td>
<td>Tarceva™ Pemetrexed Docetaxel</td>
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Molecular-targeted agents under investigation in lung cancer

Phase I
- Gefitinib
- Tarceva
- AZD2171
- Bortezomib
- Vandetanib
- Motesanib
- Sorafenib
- Avastin
- Matuzumab
- Cetuximab
- Bexarotene
- Celecoxib
- Sunitinib
- AS1404
- ABT-751

Phase II
- Lapatinib
- Panitumumab
- Cetuximab
- Tarceva
- Sunitinib
- Vatalanib
- VEGF TRAP
- Vandetanib
- Motesanib
- Sorafenib
- Celecoxib
- AZD6244

Phase III
- HKI-272
- Imatinib
- PF-3512676
- Tarabosib
- Bortezomib
- Celecoxib
- AS1404
- AZD6244

Approved

Other molecular-targeted therapies

Angiogenesis inhibitors

EGFR/HER inhibitors

HKI-272
Conclusions of Targeted Therapies of NSCLC

- There is a cause for great optimism among lung cancer physicians
  - progress is being made and has accelerated in recent years

- The search for improved treatment options continues
  - US NCI clinical trials database details
    - 479 ongoing studies in NSCLC
    - 138 ongoing studies in small-cell lung cancer

- These studies will assist our understanding of
  - how best to use currently available agents
  - what role new agents can play
Thank You for Your Attention

Terima Kasih

I miss my lung. Bob.

Xie Xie