Targeted Therapy:
Novel Approaches to Cancer Treatment

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The 1st Asia Pacific Oncology Pharmacy Congress
(APOPC)
August 5, 2006
Bangkok, Thailand

Targeted Therapy in Oncology

- Cancer is the most common cause of death
- Ineffective and incurable treatment in many cancers
- Conventional antineoplastic agents lack specificity
  causing normal tissue toxicities
- Specific, effective, and safer agents are needed
- Progress in molecular oncology defines specific anticancer targets
- Targeted therapy is clinically available

Targeting the Tumor and Its Microenvironment

Targets of Cancer Therapy

Why Epidermal Growth Factor and Receptor are Important Targets?

- Most cancers are epithelial in origin, so called carcinoma.
- Hallmark of cancer is abnormal/uncontrolled growth.
- Cancer growth is controlled by growth factors/receptors.
- Major growth factor is epidermal growth factor (EGF).
- First discovery by John Mendelsohn

Development of Targeted Therapy in Oncology

<table>
<thead>
<tr>
<th>Agents</th>
<th>FDA Approval</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>2001, 2001</td>
<td>CML, GIST</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>2004, 2003</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2005, 2004</td>
<td>Advanced colorectal cancer</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>2005, 1998</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2005, 1998</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>2004</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>2005, 2006</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2006</td>
<td>Renal cell carcinoma, Refractory GIST</td>
</tr>
</tbody>
</table>
Growth Factors and Tumor Growth and Metastasis

- Mutations in HER family
- VEGF
- MMPs
- ras
- p53
- COX-2

Tumor effects
- metastasis
- proliferation
- loss of apoptosis
- infinite replication

Angiogenesis

Invasion

Biologic Control of Tumor Growth

Mutations in
- HER family
- VEGF
- MMPs
- ras
- p53
- COX-2

Primary tumor

Metastasis

Invasion

Autocrine factors

Receptors

Paracrine factors

Normal cells

Anticline

Tumor cell

Host stromal epithelium

Tumors with HER1/EGFR Dysregulation

- Colorectal
- Lung (NSCLC)
- Head and neck
- Breast
- Esophage
- Gastric
- Pancreatic
- Ovarian
- Prostate
- Bladder
- Cervical
- Prostate
- Colorectal
- Renal
- Lung

The HER Family of Receptors

- EGF
- TGF-
- Amphiregulin
- Betacellulin
- HB-EGF
- Epiregulin

HER1/EGFR

HER2

HER3

HER4

EGFR is expressed in a variety of solid tumors

- Colorectal cancer: 75-80%
- Head and neck cancer: 90-100%
- Lung cancer (NSCLC): 40-60%
- Breast cancer: 14-41%
- Colorectal cancer: 35-70%
- Prostate cancer: 50-80%

Effects of HER1/EGFR Activation

- Src
- PLCγ
- GAP
- Grb2
- Shc
- Nck
- Vav
- Grb7
- Crk

Proliferation, invasion, metastasis, angiogenesis, and inhibition of apoptosis

HER1/EGFR and Proliferation

- HER1/EGFR signaling increases cyclin D level
- Cyclin D is a critical G1 checkpoint protein

Common Approaches to Targeting HER1/EGFR

- Anti-HER1/EGFR-blocking antibodies
- Anti-ligand-blocking antibodies
- TK inhibitors
- Ligand-toxin conjugates
- Antibody-toxin conjugates

HER1/EGFR Dysregulation in Tumors

- Ligand overproduction (autocrine loop)
- Mutations conferring constitutive activation
- Defective internalization or downregulation

HER1/EGFR Inhibitors: Mode of Antitumor Activity

- Monoclonal antibody
- TK inhibitor
- Proliferation
- Invasion
- Metastasis
- Angiogenesis
- Apoptosis
- Sensitivity to radiotherapy
- Adhesion

Therapeutic Needs in NSCLC

- Improved survival
- Improved disease-related symptoms/quality of life
- Better tolerated regimens
- Effective agents for patients not suitable for chemotherapy
- Longer time to disease progression

Rationale for HER1/EGFR as a target for anticancer drug development

- HER1/EGFR is frequently dysregulated in carcinomas
- HER1/EGFR activation initiates a signal transduction cascade that promotes tumour-cell proliferation and survival
- Overexpression/dysregulation of HER1/EGFR is associated with poor prognosis
- Overexpression of HER1/EGFR can transform cells in a ligand-dependent manner
- HER1/EGFR blockade inhibits tumourigenicity
### Treatment Options for Advanced NSCLC

<table>
<thead>
<tr>
<th>1st line</th>
<th>2nd line</th>
<th>3+ line</th>
</tr>
</thead>
<tbody>
<tr>
<td>cisplatin + paclitaxel</td>
<td>cisplatin + docetaxel</td>
<td>carboplatin + paclitaxel</td>
</tr>
<tr>
<td>cisplatin + gemcitabine</td>
<td>cisplatin + vinorelbine</td>
<td>carboplatin + paclitaxel</td>
</tr>
<tr>
<td>cisplatin + docetaxel</td>
<td></td>
<td>carboplatin + vinorelbine</td>
</tr>
</tbody>
</table>

#### 1st line
- Standard platinum based regimens

#### 2nd line
- Docetaxel
- Pemetrexate (Alimta)
- Erlotinib
- Gefitinib

#### 3+ line
- Erlotinib
- Gefitinib

---

### Erlotinib (Tarceva™)
- Erlotinib is the first and only HER1/EGFR TKI proven to significantly prolong survival in second and third line NSCLC patients.
- Erlotinib is for the treatment of patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapy regimen.
- Erlotinib is not chemotherapy.

![Erlotinib Structure](image)

**IC₅₀ = 2 nM**

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### Basic Pharmacokinetics of Erlotinib
- Bioavailability of 150mg tablet: 60%
- Tₘₚₙₐₓ: 4 hours
- Steady-state: 7-8 days
- Half-life: 36.2 hours
- Plasma protein binding: 92% to 95%
- Metabolization: liver CYP3A4
  - Ketoconazole
  - Enzyme-inducing anti-epileptic drugs
- Excretion: 83% feces

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### Erlotinib: Simple Once-Daily Dosing
- Recommended dose: 150 mg O.D.
- 2 dosages of Oral forms (film-coated tablet), 100 and 150 mg
- Take 1 tablet one hour before or two hours after meal
- Dose modifications
  - reduce to 100 mg in case of intolerable skin reactions or diarrhea
- Dose interruption
  - Erlotinib should be discontinued if ILD is diagnosed

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### Safety Profiles of Erlotinib
- Rash and diarrhea; mild and moderate grade
- ILD occurred in 0.8% of patients equal to placebo
- Asymptomatic increases in liver transaminases
- Infrequent cases of conjunctivitis, keratitis and corneal ulceration

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### Drug Interactions with Erlotinib
- Co-treatment with CYP3A4 inhibitors increases Erlotinib exposure such as
  - ketoconazole,itraconazole, clarithromycin,
  - indinavir, nelfinavir, nefazodone
- Pre-treatment with CYP3A4 inducers decreases Erlotinib exposure such as
  - rifampicin, phenytoin, carbamazepine
Phase III Randomized Study of Erlotinib versus Placebo in Advanced NSCLC Failure to Chemotherapy

**Primary Endpoint** – Survival

**Secondary Endpoint** – PFS, Response, Safety, QoL

**Randomization**

- Erlotinib* 150 mg daily
- Placebo “150 mg” daily

*2:1 Randomization

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

**Erlotinib** vs **Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (N=427)</th>
<th>Placebo (N=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1%</td>
<td>N/A</td>
</tr>
<tr>
<td>Partial response</td>
<td>8%</td>
<td>N/A</td>
</tr>
<tr>
<td>Stable disease</td>
<td>35%</td>
<td>27%</td>
</tr>
<tr>
<td>Progression</td>
<td>38%</td>
<td>57%</td>
</tr>
<tr>
<td>Inevaluable / Not assessed</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Response duration</td>
<td>7.9 mo (95% CI 5.7-10.6)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Phase III Study of Erlotinib vs Placebo in Advanced NSCLC Failure to Chemotherapy**

**Response Rate** (N=638)

- Placebo (N=211)
  - 7.9 mo (95% CI 5.7-10.6)
- Erlotinib (N=427)
  - 18% Inevaluable/Not assessed
  - 38% Progression
  - 35% Stable disease
  - 8% Partial response
  - 1% Complete response

**Patient characteristics predictive of response to Erlotinib (Study BR.21)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Erlotinib patients (%)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (146)</td>
<td>14.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Male (281)</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adenocarcinoma (209)</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>Other (216)</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td><strong>Prior smoking</strong></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Yes (311)</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>No (93)</td>
<td>24.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (53)</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>Other (374)</td>
<td>7.5</td>
<td></td>
</tr>
</tbody>
</table>

*Significance between subgroups

**Detection of EGFR Gene Amplification by Fluorescence in situ Hybridization (FISH Scoring)**

- Disomy
- Trisomy
- High polysomy
- Gene amplification

**Known HER1/EGFR activating mutations underlying NSCLC sensitivity to Erlotinib or Gefitinib**

- Sensitive to Gefitinib
- Sensitive to Erlotinib
- Never treated with TKI

**Overall Survival & Progression Free Survival**

- Overall Survival
- Progression Free Survival


### Phase III Study of Erlotinib vs Placebo in Advanced NSCLC Failure to Chemotherapy (Study BR.21)

#### Adverse Events (%)

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (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>

### Safety of Erlotinib

- Erlotinib at 150mg/day (the maximum tolerated dose) was well tolerated
- Rash and diarrhoea were the most common adverse events and were generally mild or moderate in severity
- 10% of Erlotinib-treated patients had dose reductions due to rash and 7% had dose interruptions >7 days
- Although incidence of pulmonary infection was higher in the Erlotinib group, the incidence of pulmonary infections per patient week was the same as for the placebo group
- Only 5% of patients discontinued Erlotinib due to related adverse events (2% in the placebo arm)

### Summary of BR.21 Study

- This is the first placebo controlled randomized trial to confirm that an oral tyrosine kinase inhibitor of EGFR can prolong survival
- Treatment with erlotinib was associated with significantly
  - longer overall survival
  - longer progression free survival
  - improved lung cancer-related symptoms
  - improved QoL

### Comparison of Erlotinib versus Chemotherapy in Relapsed NSCLC: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Erlotinib (150mg/day)</th>
<th>Docetaxel (75mg/m^2)</th>
<th>Pemetrexed (500mg/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>5.9</td>
<td>7.1–8.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>7.9</td>
<td>5.3–9.1</td>
<td>4.6</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>91</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Median survival in PS 2/1 patients with 1 prior regimen (months)</td>
<td>9.42</td>
<td>9.15</td>
<td>9.45</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>8.7</td>
<td>5.7–7.3</td>
<td>8.3</td>
</tr>
</tbody>
</table>

*Results cannot be compared directly because of different patient populations
Erlotinib and chemotherapy have similar efficacy in the second-line setting

### Adverse Events of Erlotinib vs Chemotherapy

#### Outcome

<table>
<thead>
<tr>
<th>Adverse event (grade 3/4)</th>
<th>Erlotinib (150mg/day)</th>
<th>Docetaxel (75mg/m^2)</th>
<th>Pemetrexed (500mg/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>40.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>&lt;1</td>
<td>12.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Anaemia</td>
<td>&lt;1</td>
<td>4.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>&lt;1</td>
<td>0.4</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Serious haematological toxicities may require hospitalisation and blood transfusions
- No haematological toxicities reported with Erlotinib
- Main reported toxicities were rash and diarrhoea
An expanded access clinical program of Erlotinib in patients with advanced stage IIIB/IV non-small cell lung cancer in Thailand

TRUST: Erlotinib Lung Cancer Survival Treatment

Narin Voravud M.D.
Vichien Srimuninnimit M.D.
Pornchai Jonglertham M.D.

Protocol: Objectives

Primary
- To provide Erlotinib to patients with advanced stage IIIB/IV Non Small Cell Lung Cancer

Secondary
- Response Rate
- Time to Progression
- Safety (SAEs and Adverse Events leading to premature withdrawal, unexpected erlotinib-related AEs and erlotinib-related rash)
- Survival
- Correlation of EGFR expression rate (HER1) and other markers potentially predictive for response

Tumour Response

<table>
<thead>
<tr>
<th>Best response</th>
<th>N = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>16</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
</tr>
<tr>
<td>Not done</td>
<td>5*</td>
</tr>
</tbody>
</table>

* 2 cases has not reached the evaluation
  * 2 cases were SAE (pulmonary emboli, sudden death)

Median Time to Disease Progression & Overall Survival

Erlotinib - Related Rash

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>•Macular or papular eruption or erythema</td>
<td>•Macular or papular eruption or erythema</td>
<td>•Severe, generalised erythroderma or macular,papular,vascular erosion</td>
</tr>
<tr>
<td>•No symptom</td>
<td>•Pruritis or other symptoms</td>
<td>Grade 4</td>
</tr>
<tr>
<td>2A - Symptomatic but tolerable</td>
<td>2B - Symptomatic, interfere daily life</td>
<td>•Generalised erosive, ulcerative,bulose dermatitis</td>
</tr>
</tbody>
</table>

Grade 1,2 = 93% (28/30) Grade 3,4 = 3% (1/30)
Management of Erlotinib-Related Rash

**Primary rash**
- Treatment
  - Topical corticosteroids
  - Analgesia

**Secondary infected rash**
- Prevention
  - Intranasal mupirocin (apply O.D.)
- Treatment
  - Topical antibiotics (clindamycin)
  - Oral antibiotics (minocycline)
  - Topical mupirocin for S.aureus

**Recommendations**
- Emollient cream
- Sunscreen
- Evaluate 1-2 wks
- Prohibit topical retinoids and benzoyl peroxide
- Unresponsive -> Dose reduction or interruption

Management of Erlotinib-Related Diarrhoea

- 4 mg Loperamide at onset of symptom
- 2 mg Loperamide every 2-4 hrs

Unresponsive to loperamide
- Dose reduction or interruption

---

**Phase III studies of Gefitinib (ISEL): Survival**

- Gefitinib vs Placebo
- Median survival: Gefitinib 5.6 months, Placebo 5.1 months
- 1-year survival: Gefitinib 27%, Placebo 20%
- Overall survival: Gefitinib vs Placebo, HR = 0.89 (0.78, 1.03), p = 0.087
- Median survival (months) 5.6 for Gefitinib, 5.1 for Placebo
- 1-year survival (%) 27 for Gefitinib, 20 for Placebo

**Study BR.21 Overall survival of Erlotinib VS Placebo**

- 42.5% improvement in median survival
- Erlotinib: 6.7 months, Placebo: 4.7 months
- 1-year survival (%) 31 for Erlotinib, 21 for Placebo
- HR* = 0.73, p<0.001

**Phase III studies of Erlotinib and Gefitinib: Results**

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (n=731)</th>
<th>Gefitinib (n=1692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>HR=0.73 (p=0.001)</td>
<td>HR=0.89 (p=0.087)</td>
</tr>
<tr>
<td>Erlotinib 6.7 months</td>
<td>Gefitinib 5.6 months</td>
<td></td>
</tr>
<tr>
<td>Placebo 4.7 months</td>
<td>Placebo 5.1 months</td>
<td></td>
</tr>
</tbody>
</table>

**Subset analysis**
- Evidence of survival benefit in never-smokers and patients of Asian origin
- Evidence of survival benefit in adenocarcinoma: Gefitinib vs Placebo, HR=0.66, p=0.089
- No survival benefit in squamous cell carcinoma

Targeted Therapy in Lung Cancer

**Thailand**
- Erlotinib has approved in 2nd and 3rd line NSCLC treatment.
- Gefitinib has approved only in 3rd line NSCLC treatment.

**USA**
- Erlotinib has approved in 2nd and 3rd line NSCLC treatment.
- Gefitinib is no longer for new patients.

**EMEA**
- Erlotinib has approved in 2nd and 3rd line NSCLC treatment.
- Gefitinib has not approved.

Chromatin Remodeling: Histone Modifications

Targeting Histone Modifying Enzymes in Cancer Treatment

**HAT / HDAC and Gene Expression**

Growth Factors and the mTOR Pathway

**Human Epidermal Growth Factor Receptor-2 (HER-2) Positive Breast Cancer**
- 20% of Breast Cancer
- Aggressive disease with short survival
- Resistance to several chemotherapy
- Response to anti HER-2 antibody (Trastuzumab)

<table>
<thead>
<tr>
<th>Median survival</th>
<th>HER2 positive</th>
<th>HER2 negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>3 years</td>
<td>6–7 years</td>
</tr>
</tbody>
</table>

Trastuzumab (Herceptin®): Humanized Anti-HER2 Antibody

- Targets HER2 protein
- High affinity ($K_d = 0.1\,\text{nM}$) and specificity
- 95% human, 5% murine
- Decreases potential for immunogenicity
- Increases potential for recruiting immune effector mechanisms

**Human**

Slamon DJ et al. Science 1987;230:177-82
Trastuzumab plus Chemotherapy in Advanced Breast Cancer Improves Survival

*Anticancer Drugs.* 2001;12:S3–10

1.0
0.8
0.6
0.4
0.2
0

Time (months)

0         5        10       15       20        25       30      35       40        45      50

Probability of survival

40%

Trastuzumab + paclitaxel
Paclitaxel

Trastuzumab plus a Taxane in HER-2 Positive Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Slamon*</th>
<th>Marty*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H + P</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>(n=68)</td>
</tr>
<tr>
<td>49.0</td>
<td>17.0</td>
</tr>
<tr>
<td>TTP (months)</td>
<td></td>
</tr>
<tr>
<td>OS (months)</td>
<td></td>
</tr>
</tbody>
</table>

ORR = objective response rate
TTP = time to disease progression
OS = overall survival


*Baselga J. Oncology 2001;61(Suppl. 2):14–21


Adjuvant Trastuzumab Efficacy in Early Breast Cancer: Disease Free Survival

HERA Combined analysis BCIRG 006 AC DH BCIRG 006 DCarboH FinHER VH / DH CEF

Median follow-up

1 year 2 years 2 years

Favours Favours no
Hercin Hercin H


Angiogenesis is involved throughout tumour formation, growth and metastasis

Stages at which angiogenesis plays a role in tumour progression


Tumour characteristics and environment promote VEGF expression

Agents inhibiting angiogenesis through the VEGF pathway
Summary: mechanism of action of anti-VEGF therapy

Inhibition of VEGF may act against tumours in three ways:
- regression of existing microvasculature
- normalisation of mature vasculature
- inhibition of production of new vasculature

Phase III trial of IFL ± Bevacizumab in metastatic Colorectal Cancer: survival

<table>
<thead>
<tr>
<th>Survival (months)</th>
<th>IFL + placebo: 15.6 (95% CI: 14.3–17.0) vs IFL + Bevacizumab: 20.3 (95% CI: 18.5–24.2) HR=0.66 (95% CI: 0.54–0.81) p&lt;0.001</th>
</tr>
</thead>
</table>

CI = confidence interval
HR = hazard ratio

Targeted Therapy in Colorectal Cancer

Bevacizumab

Approved Indication
- First-line treatment in combination with 5FU-based chemotherapy for advanced colorectal cancer

Adverse events
- Hypertension
- Proteinuria
- GT perforation, bleeding

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August 5, 2006
Bangkok, Thailand

Future Perspectives of Targeted Therapy

Narin Voravud, M.D.
Medical Oncology Unit, Department of Medicine, Faculty of Medicine, Thai Red Cross Society and King Chulalongkorn Memorial Hospital, Chulalongkorn University
Bangkok, Thailand

Published Randomized Trials of Targeted Therapy in Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Targeted Agent</th>
<th>Chemotherapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Gefitinib</td>
<td>Paclitaxel+Carboplatin</td>
<td>No benefit</td>
</tr>
<tr>
<td>EGFR</td>
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<td>Benefit in non-smokers</td>
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<tr>
<td>EGFR</td>
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<tr>
<td>Metalloproteinase</td>
<td>AG 3340</td>
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<td>Metalloproteinase</td>
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<td>Lonafinib</td>
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Published Randomized Trials of Targeted Therapy in Non-Small Cell Lung Cancer

<table>
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<tr>
<th>Target</th>
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<th>Chemotherapy</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>EGFR</td>
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<tr>
<td>Retinoid X Receptor</td>
<td>Bexarotene</td>
<td>Paclitaxel+Carboplatin</td>
<td>Response Rate</td>
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<td>Vascular Endothelial Growth Factor</td>
<td>Bevacizumab</td>
<td>Paclitaxel+Carboplatin</td>
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Ongoing Randomized Trial of Erlotinib in Non–Small Cell Lung Cancer

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<th>NSCLC Stage</th>
<th>Treatment after chemotherapy</th>
<th>N (num)</th>
<th>Adjuvant treatment</th>
<th>(EGFR+)</th>
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<th>Advanced NSCLC (EGFR+)</th>
<th>Advanced NSCLC (EGFR+)</th>
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</tr>
</tbody>
</table>

**First-line phase III trial of Erlotinib sequencing with chemotherapy**

- Chemotherapy: Gemcitabine + cisplatin
  - 6 cycles

**Erlotinib/bevacizumab phase I/II combination trial: rationale**

**Phase III trial of bevacizumab plus Erlotinib in NSCLC**

- Bevacizumab 15mg/kg plus chemotherapy
- Erlotinib 150mg/day

**Conclusions**

- Progress in molecular oncology has identified potential targets for cancer treatment.
- Targeted therapy becomes new standard treatment in oncology.
- Survival benefits are achievable with Erlotinib, Trastuzumab, and Bevacizumab.
- Combined chemotherapeutic therapy or new targeted therapy to different or many targets are under active investigation.

**Thank you for your attention**