EGFR in Gastric Cancer

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Agenda

• Brief introduction to the EGFR.
• Rationale to target the EGFR in gastric and other upper GI cancers.
• Summary of key preclinical studies.
• Summary of key clinical studies.
• New directions.
The Hallmarks of Cancer

Hanahan and Weinberg, Cell 2000
The HER Family

Ligand binding

Transmembrane

Tyrosine kinase

erb-b1 EGFR HER1
neu Erb-b2 HER2
Erb-b3 HER3
Erb-b4 HER4

TGFα EGF Epi β-cel HB-EGF Amp

HRG (NRG1)
Epi HB-GF NRG1 NRG2 NRG3 NRG4

HB-EGF Amp

EGF HRG (NRG1) Epi β-cel HB-EGF

EGF HRG (NRG1) Epi β-cel HB-EGF

Tyrosine kinase Ligand binding Transmembrane
HER1/EGFR Signaling: Survival, Proliferation, Angiogenesis

HER1/EGFR

Signal cascades

Signaling cascades

Nucleus

Gene activation

Cell cycle progression

MYC

FOS

JUN

G1

G2

S

P = phosphate group.

Current Clinical Approaches Targeting HER1/EGFR

Anti-HER blocking antibodies

Tyrosine kinase inhibitors

Adapted from Noonberg and Benz. Drugs. 2000;59:753.
Prognostic Implications of EGFR Expression in Gastric Cancer

• Conflicting results.
• Song et al at ASCO 2003
  – 665 patients
  – 25 % EGFR positive.
  – Related to:
    • Higher grade.
    • Diffuse histological type.
    • Nerve invasion.
• Not associated with outcome.
Relationship Between EGFR Expression (IHC) and Sv

Gamboa-Dominguez et al, Modern Path 2004
## Multivariate Analysis

Hazard Ratio for Not Surviving, Univariate Predictors Adjusted for Clinical Co-Variates*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of p53 Mutation</td>
<td>0.453</td>
<td>0.187 to 1.1</td>
<td>0.079</td>
</tr>
<tr>
<td>EGF-R IRS Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 1</td>
<td>1</td>
<td>Baseline Hazard</td>
<td></td>
</tr>
<tr>
<td>2 to 5</td>
<td>1.29</td>
<td>0.274 to 6.08</td>
<td>0.747</td>
</tr>
<tr>
<td>6 to 9</td>
<td>3.55</td>
<td>0.944 to 13.4</td>
<td>0.061</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>8</td>
<td>1.83 to 35</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Age, Gender, Protocol, Barrett’s Metaplasia, Tumor Location, Tumor Histology, Tumor Differentiation

Gibson et al. CCR 2004
Survival by EGF-R IRS Score

Proportion of Patients

Analysis Time in Days

IRS Score <=1
IRS Score 2-5
IRS Score 6-9
IRS Score >9

Gibson et al. CCR 2004
# Selected HER Tyrosine Kinase Inhibitors in Clinical Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Molecule/Binding</th>
<th>Specificity</th>
<th>Selected Tumor Types</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (Iressa®) AstraZeneca</td>
<td>Anilinoquinazoline Reversible</td>
<td>HER1 TK</td>
<td>Locally advanced or metastatic NSCLC, H&amp;N, breast, ovarian, prostate, pancreatic, colorectal, glioma</td>
<td>Approved*</td>
</tr>
<tr>
<td>Erlotinib (Tarceva™) Genentech, Inc.</td>
<td>Anilinoquinazoline Reversible</td>
<td>HER1 TK</td>
<td>Locally advanced or metastatic NSCLC, H&amp;N, breast, ovarian, prostate, pancreatic, colorectal, glioma</td>
<td>Approved</td>
</tr>
<tr>
<td>EKB-569 Wyeth-Ayerst Pfizer Inc</td>
<td>3-cyanoquinoline Irreversible</td>
<td>HER1/2 TK</td>
<td>NSCLC, breast, other HER-dysregulated solid tumors</td>
<td>I/II</td>
</tr>
<tr>
<td>Canertinib Pfizer Inc</td>
<td>Anilinoquinazoline Irreversible</td>
<td>HER1,2,4 TK</td>
<td>NSCLC, breast, other HER-dysregulated solid tumors</td>
<td>I/II</td>
</tr>
<tr>
<td>Lapatinib GlaxoSmithKline</td>
<td>6-thiazolylquinazoline Reversible</td>
<td>HER1/2 TK</td>
<td>NSCLC, breast, H&amp;N and other HER-dysregulated tumors</td>
<td>II</td>
</tr>
</tbody>
</table>
## Phase II Studies of Gefitinib in Gastric Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th># pts</th>
<th>Dose (mg)</th>
<th>RR (%)</th>
<th>Disease Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doi et al</td>
<td>72</td>
<td>250 and 500</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Ferry et al</td>
<td>27</td>
<td>250</td>
<td>13</td>
<td>42</td>
</tr>
</tbody>
</table>
## Phase II Studies with Erlotinib in Gastric Cancer and Esophageal Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th># pts</th>
<th>RR (%)</th>
<th>Disease Control (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tew et al</td>
<td>20</td>
<td>15</td>
<td>55</td>
<td>Esoph Ca SCCC</td>
</tr>
<tr>
<td>Dragowich et al</td>
<td>70</td>
<td>11</td>
<td>NA</td>
<td>All responses in GEJ Tumors</td>
</tr>
</tbody>
</table>
## Selected Anti-EGFR Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Pharmaceutical Company</th>
<th>Type</th>
<th>Origin</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>Merck KGaA/BMS/Imclone</td>
<td>IgG1</td>
<td>Chimeric mAb</td>
<td>III</td>
</tr>
<tr>
<td>ABX-EGF</td>
<td>Amgen/Abgenix</td>
<td>IgG2</td>
<td>Human mAb</td>
<td>II/III</td>
</tr>
<tr>
<td>EMD72000</td>
<td>Merck KGaA</td>
<td>IgG1</td>
<td>Humanized mAb</td>
<td>II</td>
</tr>
<tr>
<td>H-R3</td>
<td>York Medical Bioscience Inc.</td>
<td>IgG1</td>
<td>Humanized mAb</td>
<td>I/II</td>
</tr>
</tbody>
</table>
Stratified by:
- Center
- PS (0/1 vs 2)
- Stage of disease (locally advanced vs distant metastases)

**Study Schema**

Moore et al. ASCO GI 2005
Overall Survival for All Patients

- Adjusted for PS, pain and disease extent at randomization

HR = 0.81*
95% CI 0.67 – 0.97
P = 0.025

Survival (months)

Survival probability

Gemcitabine + Erlotinib
Median = 6.37 mon
N = 285

Gemcitabine + Placebo
Median = 5.91 mon
N = 284

* Adjusted for PS, pain and disease extent at randomization
Phase II Study of Gemcitabine + Cetuximab

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>61</td>
</tr>
<tr>
<td>RR</td>
<td>12.2 %</td>
</tr>
<tr>
<td>Median Sv</td>
<td>7.1</td>
</tr>
<tr>
<td>12 mo Sv</td>
<td>31.7 %</td>
</tr>
<tr>
<td>Grade 3-4 toxicity</td>
<td></td>
</tr>
<tr>
<td>39 % Neutropenia</td>
<td></td>
</tr>
<tr>
<td>17 % Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>22 % Asthenia</td>
<td></td>
</tr>
</tbody>
</table>

Xiong et al. JCO 2004
Advanced Pancreatic Cancer Patients

Randomize

<table>
<thead>
<tr>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine/Cetuximab</td>
</tr>
</tbody>
</table>

Enrollment started June 2004: Target 704 pts
Future Directions

• Predicting patients response to these agents.

• Integration with existing treatments.

• Combinations with other targeted agents.
Clinical Factors Predicting a Favorable Outcome with EGFR TKI in NSCLC

- Adenocarcinoma vs other NSCLC.
- Adenocarcinoma with BAC features vs other adenocarcinomas.
- Female gender.
- Performance status.
- Never smoker.
- Development of drug induce rash.

Miller et al. JCO 2004; Perez Soler et al. JCO 2004
Biological Factors Predicting a Favorable Outcome

- EGFR mutations.
- Lack of k-Ras mutations.
- EGFR copy number.
- EGFR polymorphisms.
- Akt expression and activation.
- EGFR expression.
- EGFR dynamics.
Future Directions

• Predicting patients response to these agents.

• Integration with existing treatments.

• Combinations with other targeted agents.
Cytotoxic Chemotherapies
Target S, G\textsubscript{2}, and M Phases

DNA synthesis

Late G\textsubscript{1}/S phases

Antimetabolites

S phase

Alkylating agents

Intercalating/crosslinking agents

S/G\textsubscript{2} phases

DNA transcription

DNA duplication

Mitosis

G\textsubscript{2}/M phases

Microtubule inhibitors

Erlotinib Preexposure Abrogates G₂/M Blockade Effect of Paclitaxel in H322 Cells

No Treatment  Paclitaxel  Erlotinib Followed by Paclitaxel

HER1/EGFR Inhibitors: Schedule-Dependent Interactions with Chemotherapy

- No survival benefit of HER1/EGFR-targeting TKIs given concurrently with chemotherapy
  - INTACT 1/2: gefitinib with gemcitabine/cisplatin or paclitaxel/carboplatin
  - TALENT: erlotinib with gemcitabine/cisplatin
  - TRIBUTE: erlotinib with paclitaxel/carboplatin

- In vitro effect of different schedules when combining HER1/EGFR inhibitors with conventional chemotherapy
  - Erlotinib preexposure abrogated the G₂/M effect of paclitaxel
  - Cetuximab preexposure abrogated the G₂/M effect of paclitaxel
  - Choice of schedule in combining HER1/EGFR-targeting agents in chemotherapy may be important
  - Further studies required to evaluate hypothesis

Pulsatile Administration of HER1/EGFR TKI Is More Effective Than Continuous Dosing

ZD1839 = gefitinib; PTXL = paclitaxel.

Future Directions

- Predicting patients response to these agents.
- Integration with existing treatments.
- Combinations with other targeted agents.
<table>
<thead>
<tr>
<th>Indirect</th>
<th>Direct</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER1/EGFR inhibitors</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Inhibit synthesis of angiogenic protein, VEGF</td>
<td>Prevents endothelial cells from responding to multiple angiogenic proteins, eg, bFGF, VEGF, IL-8, PDGF</td>
</tr>
</tbody>
</table>

VEGF = vascular endothelial growth factor; bFGF = basic fibroblast growth factor; IL-8 = interleukin-8; PDGF = platelet-derived growth factor.

*Personal communication, Roy Herbst, MD, PhD.*
Phase I/II Trial of Erlotinib and Bevacizumab for Recurrent NSCLC: Schema

- Phase I dose established in Phase I, although no true dose-limiting toxicities observed.

End Points
Primary: efficacy, tolerability

- Phase II dose established in phase I, although no true dose-limiting toxicities observed.

KPS = Karnofsky performance status.

Phase I/II Trial of Bevacizumab Plus Erlotinib in Recurrent NSCLC: Overall Antitumor Activity*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>26 (65)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>

*Defined by RECIST (n=40).

A431. Erlotinib induced short-lasting growth arrest, and cetuximab prompted a more delayed tumor control. The combination was superior in terms of tumor growth arrest, and cetuximab significantly decreased EGFR levels.

Growth evaluation of A431 cell line in vivo. Mice were treated with vehicle (♦), erlotinib (■), cetuximab (▲), or a combination of both (×) during 14 days. ELISA assessment of EGFR protein content is shown beside.

Jimeno et al, CR 2005
EGFR-Erk Dual Inhibition

![Graph showing T/C values for Panc 163, Panc 185, Panc 294, Panc 215, and Panc 410 under control, Erlotinib, CI-1040, and combination treatments.]

![Images of tissue samples for control, Erlotinib, CI-1040, and combination treatments.]
Conclusions

• EGFR may be a relevant target in gastric cancer.
• Prognostic implication not clear.
• Studies thus far are limited.
• Future directions include:
  – Prediction of outcome.
  – Combination with existing and new treatments.
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