Unraveling the Molecular Basis of Cancer

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Molecular Basis of Cancer

Understand the complexity of cancer and appropriately identify potential targets for therapeutic intervention

- Causes of cancer
- Process of malignant transformation
- Cell cycle control
- Roles of angiogenesis and growth factors
- Effects of tyrosine kinase inhibition
### Biology of Cancer

**Cancer by the Numbers 2006**

**United States Estimated Cancer Deaths**

<table>
<thead>
<tr>
<th></th>
<th>Men (291,270)</th>
<th>Women (273,560)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td>32.2%</td>
<td>26.8%</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td>25.8%</td>
<td>22.3%</td>
</tr>
<tr>
<td>GU</td>
<td>15.6%</td>
<td>15%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4.3%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>CNS</td>
<td>2.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Skin</td>
<td>2.4%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Others</td>
<td>13.4%</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

Biology of Cancer

Abbreviated List of the Usual Suspects

- **Chemicals**
  - Hydrocarbons: benzopyrene, benzene compounds, 2-naphthylamine
  - Asbestos & tobacco exposures
- **Radiation exposure**
- **Tumor viruses**
  - DNA: HBV, SV40/polyoma, HPV16, HAV5, HSV-8, Shope fibroma virus
  - RNA: RSV, HTLV-1
- **Cellular oncogenes**
  - myc, erbB, int-1,2,3; p53, GM-CSF, IL-2, IL-3, k-ras, Cyc-D1 & D2

Biology of Cancer

A Learning Curve That Never Plateaus

- Process of malignant transformation
  - Accumulation of multiple genetic alterations
    - Escape from normal growth control
    - Evade from apoptotic program
    - Induction of sustained angiogenesis
    - Enhanced ability to metastasize
    - Ability to invade healthy tissues
- Identification of more than 300 cancer genes
  - Signal transduction, cell cycle progression, apoptosis, angiogenesis and invasion
- A very complex system

Identification of more than 300 cancer genes

A very complex system
Biology of Cancer

Cell Cycle Control

G1/S DNA Checkpoint

G2/M DNA Damage Checkpoint

Biology of Cancer

*p53 and Cell Death*

- Transcription blockage
- Hypoxia
- Oncogene
- Radiation
- Missing nucleotides

- DNA repair
- Inhibition of angiogenesis
- Apoptosis
- Cell cycle arrest
- Proliferation
- Senescence

Courtesy of Dr. H. Tran.
Biology of Cancer

Angiogenesis

- Angiogenesis: formation of new blood vessels
- Heterotypic signaling and interactions\(^1\)
  - Mitogenic growth factors: HGD, TGF-a, PDGF
  - Growth-inhibitory signals: TGF-b
  - Trophic factors: IGF-1 & -2
- Tumor — “a wound that never heals”\(^2\)
- Observation: cancer cells located > 0.2 mm from capillaries stop growing and become apoptotic or necrotic\(^3,4\)

Biology of Cancer — Invasion and Metastasis

The Angiogenic Switch

- Tumor secretion of angiogenic factors stimulates angiogenesis
- Neovascularization
  - Makes rapid tumor growth possible by supplying oxygen and nutrients and removing waste
  - Facilitates metastasis

Biology of Cancer

ErbB/HER Receptor Tyrosine Kinases

**Rationale for Combining Inhibitors of EGFR and VEGFR**

*Targeting Both the Tumor and Endothelial Cells*

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Angiogenic Inhibition</th>
<th>VEGFR Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Inhibits tumor cell growth and blocks synthesis of angiogenic proteins (e.g., EGFR, bFGF, VEGF, TGF-α) by tumor cells</td>
<td>Inhibits endothelial cells from responding to the angiogenic protein VEGF</td>
</tr>
</tbody>
</table>

Current Biologic Agents Shopping List

- **Signal transduction/cell-cycle inhibitors**
  - VX-680
  - **Vorinostat**
  - Decitabine
  - **Bortezomib**
  - Dasatinib
  - Stat-3 inhibitors

- **Gene therapy**
  - Wild type p53
  - Antisense

- **Vaccines**
  - Tumor/dendritic cells
  - Peptides
  - Viral vaccines

- **Angiogenesis inhibitors**
  - **Bevacizumab**
  - Interferon-a/b
  - ZD6474/ZD2171
  - LY317615
  - Thrombospondin
  - VEGF-TRAP

- **Receptor-targeted therapy**
  - Multi-targeted
    - **Imatinib mesylate**
    - Sunitinib
    - Sorafenib
    - Lapatinib
  - Anti-HER2
    - Trastuzumab
  - Anti-EGFR
    - Erlotinib
    - Gefitinib
    - Cetuximab
    - Panitumumab

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*FDA approved for one or more indication.
†Gefitinib is no longer available in the US except under clinical study or when continuing on therapy.
Targeted Therapies in Cancer

Paradigm Shift?

Not a new concept
“Cytostatic vs Cytotoxic”
Modest response rates with single agents
Combination with cytotoxics?
Now with survival data
Who should receive (“Individualized”)?
Where is the best setting (early, sequential)?
Cancer is a “Chronic Disease”

Courtesy of Dr. H. Tran.
Evolution of the Modern Treatment Strategy
Personalized Cancer Medicine

Tissue screening
Proteomics
Genomics
Chemosensitivity
Mutations

Chemotherapy
Biologic therapy
Combination

Continue
Maintenance
Switch therapies

Reassess tumor response
Validated biological markers and symptoms improvement

Photos courtesy of Edward S. Kim, MD.
How Do Targeted Therapies Work?

Jon D. Herrington, PharmD, BCPS, BCOP
Hematology/Oncology Clinical Specialist
Department of Pharmacy
Scott & White Memorial Hospital
Temple, Texas
Traditional Chemotherapy Targets

- **Purine synthesis**
  - Mercaptopurine
  - Methotrexate
  - Hydroxyurea

- **Pyrimidine synthesis**
  - Ribonucleotides
    - Fludarabine, cladribine
    - Etoposide, teniposide
    - Irinotecan, topotecan

- **Deoxyribonucleotides**
  - DNA
    - Cytarabine, gemcitabine
    - Alkylating agents
    - Anthracyclines
  - RNA
    - L-asparaginase
    - Vinca alkaloids
    - Taxanes

- **Proteins**
  - Tyrosine kinase inhibitors
  - Bortezomib
  - Monoclonal antibodies

- **Enzymes, etc**
- **Microtubules**

Traditional Chemotherapy Agents

- **Advantage**
  - Activity in certain malignancies

- **Disadvantages**
  - Selectivity
    - Target rapidly dividing cells
    - Minimal efficacy in advanced disease
  - Toxicities
Targeted Therapies

- **Advantages**
  - Selectivity
    - Molecular targets
  - Toxicities
    - Decreased normal cell destruction

- **Disadvantages**
  - Unknown
    - Combinations
    - Dosing regimens
  - Long-term
  - Cost
Types of Targeted Therapies

- **Monoclonal antibodies (MoAbs)**
  - Engineered murine/human MoAbs that interact with a certain target
    - Murine
    - Chimeric
    - Humanized
    - Human

- **Tyrosine kinase inhibitors (TKIs)**
  - Small molecule inhibitors that interfere with TK activation
    - Single inhibitor
    - Multitargeted inhibitor
Targets

- Circulating targets
  - eg, VEGF
- Transmembrane targets
  - eg, EGFR, PDGFR
- Cell-membrane bound targets
  - eg, CD20, CD33
### Targets for Available Agents

**Monoclonal Antibodies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Ibritumomab tiuxetan&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CD20</td>
</tr>
<tr>
<td>Tositumomab, iodine I-131&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CD20</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin&lt;sup&gt;4&lt;/sup&gt;</td>
<td>CD33</td>
</tr>
<tr>
<td>Alemtuzumab&lt;sup&gt;5&lt;/sup&gt;</td>
<td>CD52</td>
</tr>
<tr>
<td>Cetuximab&lt;sup&gt;6&lt;/sup&gt;</td>
<td>EGFR/HER1</td>
</tr>
<tr>
<td>Panitumumab&lt;sup&gt;7&lt;/sup&gt;</td>
<td>EGFR/HER1</td>
</tr>
<tr>
<td>Trastuzumab&lt;sup&gt;8&lt;/sup&gt;</td>
<td>HER2</td>
</tr>
<tr>
<td>Bevacizumab&lt;sup&gt;9&lt;/sup&gt;</td>
<td>VEGF</td>
</tr>
</tbody>
</table>


Courtesy of Dr. J. Herrington.
## Tyrosine Kinase Inhibitors Molecular Targets

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib(^1)</td>
<td>EGFR/HER1</td>
</tr>
<tr>
<td>Erlotinib(^2)</td>
<td>EGFR/HER1</td>
</tr>
<tr>
<td>Lapatinib – investigational(^3)</td>
<td>EGFR/HER1, HER2</td>
</tr>
<tr>
<td>Imatinib(^4)</td>
<td>Bcr-abl, Kit, PDGFR</td>
</tr>
<tr>
<td>Dasatinib(^5)</td>
<td>Bcr-abl, Kit, Src family, Epha2, PDGFR(\beta)</td>
</tr>
<tr>
<td>Sorafenib(^6)</td>
<td>PDGFR(\beta), VEGFR 2 and 3, Kit, Flt3, Raf</td>
</tr>
<tr>
<td>Sunitinib(^7)</td>
<td>PDGFR(\alpha) and (\beta), VEGFR1, 2 and 3, Kit, Flt3, CSF-1R, Ret</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor; HER = human epidermal growth factor receptor; Kit = stem cell factor receptor; PDGFR = platelet derived growth factor receptor; VEGFR = vascular endothelial growth factor receptors; Flt3 = Fms-like tyrosine kinase-3; CSF-1R = colony stimulating factor receptor Type 1; Ret = glial cell-line derived neutrophic factor receptor.


Courtesy of Dr. J. Herrington.
## First-Generation TKIs and MoAbs

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Tyrosine Kinase Target</th>
<th>First-Generation Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>BCR-ABL</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors</td>
<td>KIT</td>
<td>Imatinib</td>
</tr>
<tr>
<td></td>
<td>PDGFR</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>HER2</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>EGFR</td>
<td>Erlotinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gefitinib</td>
</tr>
</tbody>
</table>
ErbB/HER/EGFR Signaling Pathway

Overexpression of a normal receptor TK (EGFR), its ligand, or both. TK receptors and their ligands can be specifically targeted extracellularly by monoclonal antibodies and intracellularly by TKIs.

EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitors.

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Expected Results from Selective MoAbs and TKIs

- Cell cycle arrest
- Apoptosis potentiation
- Angiogenesis inhibition
- Inhibition of tumor cell invasion and metastasis
- Chemotherapy and radiotherapy augmentation
Hypothetical Model for Synergism Between Cytotoxic Compounds and Bevacizumab

Mechanisms of Resistance to TKIs

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<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Tyrosine Kinase Target</th>
<th>First-Generation Inhibitor</th>
<th>Second-Generation Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>BCR-ABL</td>
<td>Imatinib</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors</td>
<td>KIT PDGFR</td>
<td>Imatinib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>HER2</td>
<td>Trastuzumab</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>EGFR</td>
<td>Erlotinib Gefitinib</td>
<td>Irreversible Inhibitors (EKB569)</td>
</tr>
</tbody>
</table>
Conclusions

- Targeted therapies have revolutionized the treatment of malignancies
- Unique mechanisms will allow for future use in combination therapies
Clinical Update: Efficacy and Safety of Targeted Therapies

Cathy Eng, MD
Assistant Professor
Department of Gastrointestinal Medical Oncology
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas
Overview

- Discuss the role of targeted therapies in solid tumors
- Discuss on-label FDA-approved agents in various malignancies
  - Colorectal
  - Lung
  - Renal
  - Breast cancer
- Side effects
- Future
  - Drugs of interest
Treatment of Metastatic Colorectal Cancer (MCRC):
anti-VEGF and EGFR Inhibition
# Efficacy of Bevacizumab (B) and Cetuximab (C) in MCRC

## Phase III Pivotal Trial Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>RR (%)</th>
<th>Median PFS or TTP (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line: Hurwitz</strong>*</td>
<td>IFL</td>
<td>35</td>
<td>6.2</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>IFL+B</td>
<td>45</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td><strong>Second-line: Giantonio</strong></td>
<td>FOLFOX</td>
<td>9</td>
<td>4.8</td>
<td>10.8</td>
</tr>
<tr>
<td>(bevacizumab-naive)†</td>
<td>FOLFOX + B</td>
<td>22</td>
<td>7.2</td>
<td>12.9</td>
</tr>
<tr>
<td><strong>Cunningham (prior irinotecan exposure)‡</strong></td>
<td>Cetuximab</td>
<td>11</td>
<td>1.5</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>Irinotecan + C</td>
<td>23</td>
<td>4.1</td>
<td>8.6</td>
</tr>
</tbody>
</table>

*RR comparison, \( P = .0024; \) PFS comparison, \( P < .001; \) OS comparison, \( P < .001.\)

†RR comparison, \( P = .007; \) PFS comparison, \( P < .05; \) OS comparison, \( P = .48.\)

‡RR comparison, \( P = .007; \) PFS comparison, \( P < .001; \) OS comparison, \( P = .48.\)

RR = response rate; PFS = progression-free survival; TTP = time to progression; OS = overall survival; IFL = irinotecan + bolus 5-fluorouracil/leucovorin; FOLFOX = infusional 5-fluorouracil/leucovorin + oxaliplatin.


Combination with intravenous 5-FU–based chemotherapy, is administered as an intravenous infusion (5 mg/kg or 10 mg/kg) every 14 days until disease progression.

- The recommended dose of bevacizumab when used in combination with bolus-IFL is 5 mg/kg.
- The recommended dose of bevacizumab when used in combination with FOLFOX-4 is 10 mg/kg.
- This announcement does not take into account the dose to be used with FOLFIRI and modified schedules of FOLFOX—ie, FOLFOX6 or FOLFOX7.

IFL = irinotecan + bolus 5-fluorouracil/leucovorin; FOLFOX = infusional 5-fluorouracil/leucovorin + oxaliplatin; FOLFIRI = 5-fluorouracil/leucovorin + irinotecan.
Facts of Approved Biologics

Metastatic Colorectal Cancer

- **Bevacizumab**\(^1\)
  - Hypertension
  - Remote risk of GI perforation
  - Reversible leukoencephalopathy syndrome
  - Patients with history of ATEs are at higher risk of recurrent event
  - q2wk or q3wk
  - Approved for front-line or bevacizumab naive

- **Cetuximab**\(^2\)
  - Acne-type rash
  - Paronychial infections
  - Electrolyte imbalance: Mg, Ca
  - Hypersensitivity reaction
  - Weekly administration
  - Approved for patients who have progressed on irinotecan or irinotecan intolerant

Gl = gastrointestinal; ATEs = arterial thromboembolic events.

Patients with advanced EGFR+ CRC and NO prior anti-EGFR or VEGF therapy (N = 1040)

N = 463

RANDOMIZATION

Panitumumab (n = 231)

BSC (n = 232)

Panitumumab (n = 174)

PD

Dose: 6 mg/kg q2wk

EGFR = endothelial growth factor receptor; CRC = colorectal cancer; VEGF = vascular endothelial growth factor; BSC = best supportive care; PD = progressive disease.

Panitumumab vs Best Supportive Care

Progression-Free Survival

Event-Free Probability vs Weeks from Randomization

Hazard ratio = 0.54
(95% CI: 0.44, 0.66)

Stratified log-rank test
P < .000000001

Patients at risk:

- Panitumumab: 231, 118, 49, 31, 13, 5, 1
- BSC: 232, 75, 17, 7, 3, 1, 1

Summary for FDA-Approved Drugs in Metastatic Colorectal Cancer (MCRC)

- IFL has been replaced by its infusional counterpart (FOLFIRI)
- Front-line MCRC: bevacizumab + 5-FU based chemotherapy (FOLFOX, FOLFIRI, or 5-FU)
- The benefits of continuing bevacizumab following progression are unknown. Given the lack of data, its use cannot be advocated following progression
- Cetuximab is approved in combination with irinotecan following progression on irinotecan or as a single agent if intolerant to irinotecan
- Panitumumab was recently approved for the treatment of MCRC (trials compared panitumumab vs BSC)
Biologics in Lung Cancer
## The Role of Small Molecule Anti-EGFR TKIs in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Median OS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTACT 1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1093</td>
<td>Gemcitabine/cisplatin x 6 cycles + 1) gefinitib 500 mg daily 2) gefinitib 250 mg daily 3) placebo</td>
<td>Arms 1&amp;2: 9.9 mo Arm 3: 10.9 mo</td>
<td>NS</td>
</tr>
<tr>
<td>INTACT 2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1037</td>
<td>Carboplatin/paclitaxel x 6 cycles + 1) gefinitib 500 mg daily 2) gefinitib 250 mg daily 3) placebo</td>
<td>Arm 1: 8.7 mo Arm 2: 9.8 mo Arm 3: 9.9 mo</td>
<td>NS</td>
</tr>
<tr>
<td>TALENT&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1172</td>
<td>1) gemcitabine/cisplatin x 6 cycles + erlotinib (150 mg daily) 2) gemcitabine/cisplatin</td>
<td>Arm 1: 9.9 mo Arm 2: 10.1 mo</td>
<td>NS</td>
</tr>
<tr>
<td>TRIBUTE&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1059</td>
<td>1) carboplatin/paclitaxel x 6 cycles+ erlotinib (150 mg daily) 2) carboplatin/paclitaxel</td>
<td>Arm 1: 10.6 mo Arm 2: 10.5 mo</td>
<td>NS</td>
</tr>
</tbody>
</table>

Erlotinib Plus Chemotherapy in NSCLC

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Erlotinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mo)</td>
<td>10.6</td>
<td>10.5</td>
</tr>
<tr>
<td>1-y survival rate (%)</td>
<td>46.9</td>
<td>43.8</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.995</td>
<td>(P = .95)</td>
</tr>
</tbody>
</table>

NSCLC = non–small cell lung cancer.
Treatment-naive stage IIIB or IV NSCLC
- No history of hemoptysis
- No CNS metastases
- ECOG PS 0–1

Carboplatin (C) AUC = 6 Paclitaxel (P) 200 mg/m² and q3wk for 6 cycles with Bevacizumab (B) 15 mg/kg (n = 434)

Primary endpoint: OS

Carboplatin (C) AUC = 6 Paclitaxel (P) 200 mg/m² and q3wk for 6 cycles (n = 444)

<table>
<thead>
<tr>
<th>RR</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>27% vs 10%  (P &lt; .0001)</td>
<td>6.4 mo vs 4.5 mo (HR = 0.62, 95% CI: 0.53, 0.72, P &lt; .0001)</td>
<td>12.5 mo vs 10.2 mo (HR = 0.77, 95% CI: 0.65, 0.93, P = .007)</td>
</tr>
</tbody>
</table>

Summary of Biologic Agents in NSCLC

- 4 large phase III studies failed to demonstrate a benefit in overall survival (OS) with the addition of gefinitib or erlotinib to standard chemotherapy
  - Subset analysis revealed that patients who are nonsmokers and Asians fared better\(^1,2\)
  - Patients with a mutation in the TK domain of the EGFR receptor have improved OS\(^3-5\)
    - Exons 18-21
  - Erlotinib is currently approved for use in surgically unresectable NSCLC patients
- Bevacizumab in combination with paclitaxel and carboplatin, was approved by the FDA (10/12/06) as first-line therapy for NSCLC

Renal Cell Carcinoma

Multitargeted Oral Agents
## Efficacy of Sunitinib in Renal Cell Carcinoma

### Phase II–III Pivotal Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>N</th>
<th>Design</th>
<th>RR (%)</th>
<th>Median PFS or TTP (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer et al(^1) (previously treated)</td>
<td>II</td>
<td>63</td>
<td>Sunitinib (50 mg/d, wk 1–4, repeat q6wk)</td>
<td>PR: 25 (40%)</td>
<td>8.7 (95% CI: 5.5–10.7)</td>
<td>16.4</td>
</tr>
<tr>
<td>Motzer et al(^2) (previously treated, clear cell only)</td>
<td>II</td>
<td>106</td>
<td>Sunitinib (50 mg/d, wk 1–4, repeat q6wk)</td>
<td>PR: 36 (34%)</td>
<td>8.3 (95% CI: 7.8–14.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Multicenter(^3) (ongoing)</td>
<td>III</td>
<td>750</td>
<td>Randomized A. sunitinib</td>
<td>PR: 103 (31%)</td>
<td>11 vs 5 HR = 0.415 (95% CI: 0.320-0.539) (P &lt; .000001)</td>
<td>Not Reached</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. IFN-A (thrice weekly)</td>
<td>20 (6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR = response rate; PFS = progression-free survival; TTP = time to progression; OS = overall survival; PR = partial response; CI = confidence interval.

Efficacy of Sorafenib in Renal Cell Carcinoma

*Pivotal Phase III Trial (TARGET)*

**Randomization**

Clear cell cancer patients, failed 1 prior therapy < 8 mo prior, ECOG PS 0–1

**Placebo** (n = 452)

**Sorafenib** (n = 200)

**Primary endpoint: OS**

<table>
<thead>
<tr>
<th>Median PFS or TTP (mo)</th>
<th>Median OS (mo): 6-mo Postcrossover</th>
<th>Median OS (mo): with Censored Placebo Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 wk vs 12 wk</td>
<td>19.3 vs 15.9 mo HR = 0.77 (95% CI: 0.63–0.95)</td>
<td>19.3 vs 14.3 mo HR = 0.74 (95% CI: 0.58–0.93)</td>
</tr>
<tr>
<td>HR = 0.44</td>
<td>P = .015</td>
<td>P = .01</td>
</tr>
<tr>
<td>(95% CI: 0.35–0.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P &lt; .000001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Associated Side Effects

**Sunitinib and Sorafenib**

### Sunitinib

1. Nausea
2. Diarrhea
3. Stomatitis
4. Hyperlipasemia
5. Neutropenia
6. Fatigue
7. Decrease in LVEF (rare)

### Sorafenib

1. Rash
2. Fatigue
3. Dyspnea
4. Hypertension

---

Summary of Biologic Agents in Metastatic Renal Cell Cancer

- Both sunitinib and sorafenib clearly have a role in previously treated renal cell cancer and are currently FDA approved.
- Additional biologic agents are currently being evaluated and have demonstrated promising activity.
Biologics in Breast Cancer
E2100

Phase III Trial of Paclitaxel +/- Bevacizumab as First-Line Therapy in Recurrent or Metastatic Breast Cancer

715 recurrent/metastatic breast cancer patients

Paclitaxel 90 mg/m² d 1, 8, 15 of 28-d cycle

Paclitaxel 90 mg/m² d 1, 8, 15 of 28-d cycle + Bevacizumab 10 mg/kg d 1, 15

Paclitaxel

(n = 316)

Response rate 14%
Overall survival 6 months

Paclitaxel + Bevacizumab

(n = 330)

Response rate 28%
Overall survival 11 months

Miller KD, et al. 41st ASCO; May 13-17, 2005. Late-breaking session.
**EGF 100151**

*Phase III Trial of Capecitabine +/- Lapatinib as Second-Line Therapy in Recurrent or Metastatic Breast Cancer*

- **Randomization**
  - 315 locally advanced or metastatic Her 2+ cancer patients with recurrent disease

- **Treatment Options**
  - Capecitabine (2000 mg/m²/d) + lapatinib (1250 mg/d), d 1–14, repeat q21d
  - Capecitabine (2500 mg/m²/d), d 1–14, repeat q21d

- **Median TTP**
  - 36.9 weeks vs 19.7 weeks

- **P-value**
  - $P = .00016$

**TTP** = time to tumor progression.

Side Effects of Lapatinib

- Diarrhea
- Palmar-plantar erythrodysesthesia
- Rash
- Decreased left ventricular ejection fraction

Both bevacizumab and lapatinib have demonstrated advantages in metastatic and recurrent breast carcinoma.

Final data have yet to be reported on both of these studies.

Neither bevacizumab nor lapatinib is currently FDA approved for this indication.
### New Agents on the Horizon in Solid Tumors

<table>
<thead>
<tr>
<th>Molecular Target</th>
<th>Name of Drug</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF-A, B, PIGF</td>
<td>VEGF Trap</td>
<td>II</td>
</tr>
<tr>
<td>VEGFR 1-3, PDGFR, c-Kit</td>
<td>AG-013736 (axitinib)</td>
<td>III</td>
</tr>
<tr>
<td>VEGFR 1-3</td>
<td>AZD 2171, GW783034 (pazopanib)</td>
<td>III</td>
</tr>
<tr>
<td>EGFR/VEGFR-2</td>
<td>ZD6474 (vandetanib)</td>
<td>III</td>
</tr>
<tr>
<td>Src Kinase</td>
<td>Dasatinib, AZD0530</td>
<td>II</td>
</tr>
<tr>
<td>mTOR</td>
<td>CCI-779 (temsirelimus), RAD001 (everolimus)</td>
<td>III</td>
</tr>
</tbody>
</table>

*Courtesy of Dr. C. Eng.*
Present and Future Role of Targeted Therapies in Cancer Care

Tarek Mekhail, MD, MSc, FRCSI, FRCSEd
Director, Lung Cancer Medical Oncology Program
Hematology/Medical Oncology
The Cleveland Clinic
Cleveland, Ohio
Drug Development Paradigm

- Identifying a therapeutic target
- Preclinical activity
- Clinical drug development
Targeted Therapy

- Anti-EGFR blocking antibodies
- Antiligand blocking antibodies
- Tyrosine kinase inhibitors
- Ligand-toxin conjugates

Adapted from Noonberg SB, Benz CC. Drugs. 2000;59:753, with permission.
Gefitinib + Paclitaxel

Response in LX-1 Lung Tumor Xenografts with Low Expression of Wild-Type HER1/EGFR

*Day 1 of treatment defined as tumor size 5–6 mm (3–5 days postimplantation).
Phase II Trial of Erlotinib in HER1/EGFR Positive Patients with Advanced NSCLC

**Efficacy**

<table>
<thead>
<tr>
<th>CR + PR</th>
<th>CR/PR + SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.3%</td>
<td>50.9%</td>
</tr>
</tbody>
</table>

N = 57

<table>
<thead>
<tr>
<th>N = 57</th>
<th>OS (mo)</th>
<th>1-y Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib 150 mg/d</td>
<td>8.4</td>
<td>40</td>
</tr>
</tbody>
</table>

OS = overall survival; CR = complete response; PR = partial response; SD = stable disease.

Phase III Trial of Erlotinib for Advanced NSCLC—Schema

Locally advanced or metastatic NSCLC
PS 0–3
≥1 failed prior chemotherapy regimen
No prior malignancies or uncontrolled CNS metastases except basal cell skin cancers
Stratified by
• Center
• PS (0/1 vs 2/3)
• Response to prior therapy (CR/PR:SD:PD)
• Prior regimens (1 vs 3)
• Prior platinum (yes vs no)
N = 731*

Randomize

Erlotinib 150 mg/d
n = 488

Placebo
n = 243

End Points
Primary: overall survival
Secondary: progression-free survival, overall response rate, duration of response, quality of life, safety

*2:1 randomization to the experimental arm.
PS = performance status; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
BR.21

Phase III Trial of Erlotinib for Advanced NSCLC—Overall Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>Overall Survival (% Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

Median Survival (mo) 1-Year Survival (%)

- Erlotinib: 6.7 31
- Placebo: 4.7 22

HR = 0.70, P < .001

HR = hazard ratio.

Adapted from Shepherd FA, et al. *N Engl J Med.* 2005;353:123, with permission from the Massachusetts Medical Society. Copyright 2005. All rights reserved.
Randomization of 2nd- or 3rd-line therapy for NSCLC

No prior EGFR, docetaxel, or pemetrexed

Multicenter Study
N = 800
Open
Primary Endpoint = Response

Docetaxel + cetuximab
Pemetrexed + cetuximab
Docetaxel
Pemetrexed

http://clinicaltrials.gov
Angiogenesis

Image courtesy of Dr. T. Mekhail.
The Angiogenic Switch Is a Key Step for Tumor Growth and Risk of Metastasis

Small tumor
- Nonvascular
- “Dormant”

Larger tumor
- Vascular
- Metastatic potential

Agents Targeting the VEGF Pathway

- Anti-VEGF antibodies (bevacizumab)
- Soluble VEGFRs (VEGF-Trap)
- Anti-VEGFR antibodies (IMC-1121b)
- Small-molecule VEGFR inhibitors
  - Vatalanib (PTK787)
  - Sunitinib (SU11248)
  - Sorafenib (BAY 43-9006)
  - ZD6474

Adapted from Podar K, Anderson KC. Blood. 2005;105:1383, with permission.
Bevacizumab

- Recombinant humanized monoclonal IgG₁ antibody¹
- Recognizes all isoforms of VEGF-A²
- Estimated half-life is approximately 20 days (range, 11–50)¹

Image courtesy of Dr. T. Mekhail.
Bevacizumab, Carboplatin, and Paclitaxel
Phase III First-Line Trial in NSCLC (E4599)

**Design**

- **Randomization**
  - CP × 6: Carboplatin AUC 6 (q3wk) + paclitaxel 200 mg/m²
  - BCP × 6: Bevacizumab (15 mg/kg q3wk) to PD + carboplatin AUC 6 (q3wk) (15 mg/kg q3wk) + paclitaxel 200 mg/m²

- No crossover allowed in this study

- **Eligibility**
  - Previously untreated stage IIIB/IV NSCLC
  - Nonsquamous NSCLC
  - No history of hemoptysis
  - No CNS metastases
  - ECOG PS 0–1
  - N = 855 eligible patients*

- **Primary end point:** overall survival
- **Secondary end points** include time-to-progression, overall response rate, tolerability

*1:1 randomization to the experimental arm.
Sandler et al. 41st ASCO; May 13-17, 2005. Abstract LBA4 and oral presentation.
Bevacizumab, Carboplatin, and Paclitaxel Phase III First-Line Trial in NSCLC (E4599)

Overall Survival

Medians: 10.2, 12.5

HR = 0.77 (0.65, 0.93)

\[ P = .007 \]

The Future

- Combination therapy
- Multitargeted agents
- Clinical markers for response
- Molecular markers for response
Bevacizumab + Erlotinib
Phase I/II Trial in Recurrent NSCLC (OSI2486)

*Overall Antitumor Activity*

<table>
<thead>
<tr>
<th>Best Response (N = 40†)</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>8 (20)</td>
</tr>
<tr>
<td>SD</td>
<td>26 (65)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>

*By RECIST criteria (N = 40).
†Total population.

Phase I/II Trial of Bevacizumab + Erlotinib in Recurrent NSCLC

Case History (Phase I)

- 48-year-old African-American male with stage IIIB adenocarcinoma with pleural effusion
- CT scans at baseline and following 2 cycles of therapy (dose level I)

Pretreatment with Bevacizumab + Erlotinib

**Multitargeted Approaches**

**ZD6474 in Advanced NSCLC**

- Orally available inhibitor of 2 key pathways in tumor growth
  - VEGFR-dependent tumor angiogenesis
  - EGFR-dependent tumor cell proliferation and survival
- Number of randomized phase II trials ongoing/completed
  - ZD6474 vs gefitinib
  - Docetaxel +/- ZD6474
  - 3 arms: ZD6474 alone vs paclitaxel/carboplatin + ZD6474 or placebo

Clinical Markers for Response BR.21
Exploratory Analysis—Survival by Smoking History

**Never Smoked**
- Erlotinib (n = 104)
- Placebo (n = 42)
- HR = 0.42 (95% CI, 0.28–0.64)
- ORR = 24.7%

**Current and Ex-smokers**
- Erlotinib (n = 358)
- Placebo (n = 187)
- HR = 0.87 (95% CI, 0.71–1.05)
- ORR = 3.9%

HR = hazard ratio; CI = confidence interval; ORR = overall response rate.

Molecular Markers for Response

- EGFR mutation status by gene sequencing
- EGFR gene copy number by fluorescence in situ hybridization
- EGFR protein expression by immunohistochemistry
Renal Cell Carcinoma

Targets of Single Agents

VEGF
VEGFR
Sorafenib
Sunitinib, Sorafenib, AG-013736

PDGF
PDGFR

TGF-a
EGFR
Sorafenib

HIF

Bevacizumab

Erlotinib

Molecular Targeted Therapies for RCC

Target Inhibition

- Sorafenib\(^1\)
  - VEGFR, PDGFR, RAF
- Sunitinib\(^2\)
  - VEGFR, PDGFR
- AG-013736\(^3\)
  - VEGFR, PDGFR
- Bevacizumab\(^4\)
  - VEGF
- Temsirolimus (CCI-779)\(^5\)
  - mTOR

TARGET Trial

Sorafenib vs Placebo Progression-Free Survival in Cytokine-Refractory RCC

- Phase III, randomized double-blind, placebo-controlled trial*
- Patients with cytokine-refractory RCC were randomized 1:1 to sorafenib (400 mg BID) or placebo
- Primary endpoint: overall survival

Median PFS†
Sorafenib (n = 451) = 24 weeks
Placebo (n = 452) = 12 weeks
Hazard ratio (S/P) = 0.44
(95% CI: 0.35, 0.55)
P < .000001

*Single planned analysis. Independently assessed.
†PFS analysis performed March, 2005 (data cut-off Jan 28, 2005).
Adapted from Escudier B., 41st ASCO; May 13-17, 2005, with permission.
TARGET Trial
Tumor Response

21 June 2005

17 October 2005

Sunitinib vs Interferon

Phase III Study Design

N = 750

Stratification factors
- LDH ≤ 1.5 vs > 1.5 x ULN
- ECOG PS 0 vs 1
- Presence vs absence of nephrectomy

Sunitinib (n = 375)

IFN alfa (n = 375)

Sunitinib vs Interferon

Progression-Free Survival

(Independent Central Review)

Sunitinib
Median: 11 months
(95% CI: 10–12)

IFN alfa
Median: 5 months
(95% CI: 4–6)

Hazard Ratio = 0.415
(95% CI: 0.320–0.539)

P < .000001

### Most Common Side Effects Associated with Marketed Targeted Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Most Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab¹</td>
<td>Asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td>Cetuximab²</td>
<td>Acneform rash, asthenia/malaise, diarrhea, nausea, abdominal pain, vomiting</td>
</tr>
<tr>
<td>Erlotinib³</td>
<td>Rash, diarrhea, anorexia, fatigue, dyspnea, cough</td>
</tr>
<tr>
<td>Gefitinib⁴</td>
<td>Diarrhea, rash, acne, dry skin, nausea, vomiting</td>
</tr>
<tr>
<td>Sorafenib⁵</td>
<td>Rash, diarrhea, hand-foot skin reaction, fatigue, hypertension, alopecia</td>
</tr>
<tr>
<td>Sunitinib⁶</td>
<td>Diarrhea, hypertension, bleeding, mucositis, skin abnormalities, altered taste</td>
</tr>
</tbody>
</table>

Raising The Bar

Toxicity Profile

- Absence of traditional side effects
- Manageable toxicity
The Future

- Overcoming evolving resistance
- Combination with other agents
- Treatment of earlier stage of the disease
- Individualizing treatment

Cure!