Clinical Breakthroughs in EGFR Inhibition

Applying the Science to Your Clinical Practice

Join the faculty after the program for a clinical chat at the OES booth!
2:30 pm – 3:00 pm, Booth #551

Friday, May 5, 2006
Luncheon program
12:30 pm – 2:00 pm

Boston Convention & Exhibition Center
Room 210, Meeting Level 2
Boston, Massachusetts

OES
A Division of the Oncology Nursing Society
Clinical Breakthroughs in EGFR Inhibition: Applying the Science to Your Clinical Practice

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This educational program has been developed and produced by OES, a division of the Oncology Nursing Society.

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Disclosure of Off-Label Uses
Some of the information contained in this program may be inconsistent with product labeling. Therefore, the official package inserts for all products mentioned should be consulted for complete prescribing information and a complete listing of indications, contraindications, warnings, precautions, adverse reactions, and dosage and administration guidelines. Healthcare providers should exercise their own independent medical judgment in making treatment decisions.
Check out CE Central, where you’ll find detailed information on all the top-notch educational programming available through ONS.

Look for the CE Central Catalog in the mail, or go online for an updated list of program offerings.

www.oesweb.org
Program Overview

What are the hottest new clinical developments in targeted therapies?

This program takes a fascinating look at EGFR inhibition, including an illustrated explanation of cellular changes, a clinical review of promising new treatments, and a comprehensive discussion of side effects and their management. Participants will leave this program with a clear understanding of how side effects correlate with treatment progression and with proven strategies to successfully manage the side effects of EGFR inhibitors.

This program uses keypads for interactive discussion and includes a patient education poster illustrating EGFR inhibition, along with other take-home tools!

Target Audience

This program is designed for oncology nurses with an interest in understanding the newest advances for targeting HER1/EGFR and in learning strategies to manage the unique side effects associated with EGFR inhibition.

Program Objectives

At the end of this symposium, the participant will be able to:
1. Discuss the implications of downregulating HER1/EGFR.
2. Summarize the therapeutic strategies for targeting HER1/EGFR.
3. Identify strategies to prepare your practice to administer HER1/EGFR inhibitors.
4. Summarize best practices for managing symptoms related to HER1/EGFR inhibitors.

Faculty

PROGRAM CHAIR
Teresa Knoop, MSN, RN, AOCN®
Clinical Nurse Specialist
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

FACULTY
Michael Morse, MD
Associate Professor of Medicine
Clinical Leader, GI Oncology
Duke University Medical Center
Durham, North Carolina

Leslie Tyson, MS, APRN-BC, OCN®
Nurse Practitioner, Thoracic Oncology Service
Memorial Sloan-Kettering Cancer Center
New York, New York
Program Outline

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 pm</td>
<td>Welcome and Program Introduction</td>
<td>Teresa Knoop, MSN, RN, AOCN®</td>
</tr>
<tr>
<td>12:35 pm</td>
<td>The Biology of HER1/EGFR: An Illustrated Approach</td>
<td>Teresa Knoop, MSN, RN, AOCN®</td>
</tr>
<tr>
<td>12:50 pm</td>
<td>Targeting HER1/EGFR: New Strategies, New Agents</td>
<td>Michael Morse, MD</td>
</tr>
<tr>
<td>1:05 pm</td>
<td>Preparing Your Practice: Nursing Implications &amp; Side Effects</td>
<td>Teresa Knoop, MSN, RN, AOCN®</td>
</tr>
<tr>
<td>1:25 pm</td>
<td>Clinical Discussion: Managing the EGFR-Inhibitor Rash</td>
<td>Leslie Tyson, MS, APRN-BC, OCN®</td>
</tr>
<tr>
<td>1:40 pm</td>
<td>Future Directions: Targeting EGFR</td>
<td>Michael Morse, MD</td>
</tr>
<tr>
<td>1:50 pm</td>
<td>Questions and Answers</td>
<td>Faculty Panel</td>
</tr>
<tr>
<td>2:00 pm</td>
<td>Program Concludes</td>
<td></td>
</tr>
</tbody>
</table>

Continuing Education Information

Participants will receive 1.8 continuing nursing education credits at the successful completion of the program. Oncology Nursing Society (ONS) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s (ANCC’s) Commission on Accreditation.

Accreditation as an ANCC provider refers only to its continuing education activities and does not imply ANCC Commission on Accreditation endorsement of any commercial products. ONS is approved as a provider of continuing education by the California Board of Registered Nursing, Provider # 2850.

The credits you earn for this program qualify for ONC-PRO points needed for ONCC certification renewal.

This session includes approximately 50 minutes of pharmacology content.

Disclosure of Significant Relationships

Faculty disclose all apparent or potential conflicts of interest with companies whose products or services are mentioned in the program to allow participants to form their own judgments about the program.

Teresa Knoop, MSN, RN, AOCN®, is a speaker for Amgen and Genentech and is on an advisory board for Bristol-Myers Squibb.

Michael Morse, MD, is a speaker for Bristol-Myers Squibb and Genentech.

Leslie Tyson, MS, APRN-BC, OCN®, is a speaker for OES educational programs supported by Genentech BioOncology.
Faculty Biographies

PROGRAM CHAIR

Teresa Knoop, MSN, RN, AOCN
Clinical Nurse Specialist
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

Teresa Knoop, MSN, RN, AOCN®, earned a BSN from Murray State University in Murray, Kentucky, and an MSN from Vanderbilt School of Nursing in Nashville, Tennessee. She is currently a clinical nurse specialist and supervisor at the Vanderbilt-Ingram Cancer Center information program, where she provides information to healthcare professionals and consumers about cancer clinical trials and services. Ms. Knoop speaks frequently on the topics of targeted therapies and supportive care, and she is a co-editor of the OES publication Oncology Supportive Care Quarterly.

FACULTY

Michael Morse, MD
Associate Professor of Medicine
Clinical Leader, GI Oncology
Duke University Medical Center
Durham, North Carolina

Michael Morse, MD, MHS, is an associate professor of medicine, clinical leader of the GI Oncology Program, and clinical director of the molecular therapeutics program at Duke University Medical Center in Durham, NC. He earned an MD from Yale University, completed internal medicine training at the University of Washington, and completed a medical oncology/hematology fellowship and Master’s of Health Science in Clinical Research at Duke University Medical Center. His areas of clinical expertise include the management of GI malignancies with a subspecialty emphasis on liver tumors and metastases.

Dr. Morse’s research involves the development of cancer vaccines and the testing of novel therapeutics including antiangiogenesis and epidermal growth factor inhibitors. He performs clinical and laboratory research in the area of anticancer immunotherapy and new drug development. His publications include books and journal articles on immunotherapy, liver cancers, and biliary disease. Dr. Morse speaks frequently on the topics of cancer immunotherapy and gastrointestinal malignancies, and he is editor of a textbook on immunotherapy and associate editor of a textbook on liver tumors.

Leslie Tyson, MS, APRN-BC, OCN®
Nurse Practitioner, Thoracic Oncology Service
Memorial Sloan-Kettering Cancer Center
New York, New York

Leslie Tyson, MS, APRN-BC, OCN®, earned a BSN in nursing from Columbia University School of Nursing and an MS, Nurse Practitioner, from the State University of New York-Stony Brook. She has been employed by Memorial Sloan-Kettering Cancer Center for 28 years, and the majority of her clinical experience has been in thoracic oncology and clinical trials. Ms. Tyson speaks frequently on the topics of targeted therapies, EGFR-tyrosine kinase inhibitors in non-small cell lung cancer, and chemotherapy-induced nausea and vomiting.

Her publications include “Patient Assessment,” in N. Houlihan (Ed.), Site Specific Cancer Series: Lung Cancer (Pittsburgh, PA: Oncology Nursing Society, 2004), and 100 Questions and Answers About Cancer Symptoms and Cancer Treatment Side Effects (Sudbury, MA: Jones and Bartlett, 2004) with Joanne Kelvin (co-author).
The Biology of HER1/EGFR: An Illustrated Approach

Teresa Knoop, MSN, RN, AOCN®
Clinical Nurse Specialist
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

Applying the Science to Your Clinical Practice

Targeted Therapies

- Targeted therapies are directed toward specific pathways:
  - Antigen
  - Growth factor
  - Receptor
  - Other molecule
- Targeted therapies moderate, control, or kill cancer cells.
Clinical Breakthroughs in EGFR Inhibition

Applying the Science to Your Clinical Practice

Signal Transduction

- Signal transduction is the communication process used by regulatory molecules to mediate essential cell processes.
  - Essential cell processes:
    - Growth
    - Differentiation
    - Survival
  - Aberrations lead to:
    - Increased proliferation, sustained angiogenesis, tissue invasion and metastases, and apoptosis inhibition
Signal Transduction

- Activation
  - Ligand binding
  - Dimerization
  - TK activation
- Downstream signaling
- Cell regulation

Terminology

- Ligands - molecules, such as growth factors, that bind to receptors
- Ligand binding - ligand attaches to receptor site and activates signaling
- Monomer - single receptor, inactivated state
- Dimerization - activation of receptor through monomer pairing
- Phosphorylate - attachment of a phosphate to a protein
Epidermal Growth Factor Receptor (EGFR/HER1)

EGFR is also known as HER1 (human EGF receptor 1).

EGFR:
- Regulates cell division, repair, and survival
- Contains an intracellular tyrosine kinase domain
- Is minimally expressed on normal cells
- Is involved in tumor metastasis

Background for EGFR

- Epidermal growth factor
  - Was discovered in the 1960s by Stanley Cohen
  - Stimulates proliferation of epidermal basal cells
- Growth factor receptors
  - The growth factor receptor was sequenced and cloned in 1984.
  - It plays a role in cell function, growth, and cellular interaction.
- Protein kinases
  - Tyrosine kinases were identified in the 1980s.

Kinases

- Kinases phosphorylate specific protein, carbohydrate, or lipid residues.
- Protein kinases are the most well-known type of kinase.
  - Serine - 1955
  - Threonine - 1960s
  - Tyrosine - 1980s
EGFR Ligands and Receptors

<table>
<thead>
<tr>
<th>Ligands</th>
<th>HER1</th>
<th>HER2</th>
<th>HER3</th>
<th>HER4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF</td>
<td>erbB1</td>
<td>erbB2</td>
<td>erbB3</td>
<td>erbB4</td>
</tr>
<tr>
<td>TGFα</td>
<td>HER1</td>
<td>HER2</td>
<td>HER3</td>
<td>HER4</td>
</tr>
<tr>
<td>Amphiregulin</td>
<td>EGFR</td>
<td>neu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB-EGF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betacellulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epiregulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heregulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Neuregulin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heregulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB-EGF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betacellulin</td>
<td></td>
<td></td>
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</tbody>
</table>

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EGFR/HER Family

Ligand growth factor

Extracellular domains that bind growth factors

Intracellular domains that transmit signals to regulate genes

Tyrosine kinase (TK) domains

Tyrosine kinase (TK) domains

No tyrosine kinase (TK) domains

Tyrosine kinase (TK) domains

Ciardello et al., 2004; Herbst, 2004; Mass, 2004; Perez-Soler, 2004a, b.

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Regions of EGFR

- Input layer
  - Extracellular, ligand binding receptor
- Signal processing layer
  - Transmembrane region
  - Homodimerization
  - Heterodimerization
- Output layer
  - Intracellular region
  - Activation of tyrosine kinase domain

Role of EGFR in Signal Transduction
Epidermal Growth Factor Receptor (EGFR)

EGFR ligand binding
In normal cells, the EGFR-TK signal is strictly regulated.

Dimerization
Cell growth is controlled.

Normal cell

Turning on the EGFR-TK signal
In tumor cells, the EGFR-TK signal is inappropriately turned on.

EGFR-TK drives uncontrolled cancer cell growth.

Proliferation
Invasion
Angiogenesis
Metastasis
Inhibition of apoptosis

Cancer cell

HER Family Dimers

Weak signaling
HER1-HER1
HER2-HER2
HER3-HER3
HER4-HER4

Homodimers

Strong signaling
HER1-HER2
HER1-HER3
HER1-HER4
HER2-HER3
HER2-HER4
HER3-HER4

Heterodimers
**Clinical Breakthroughs in EGFR Inhibition:**

**Applying the Science to Your Clinical Practice**

---

**Tyrosine Kinase Inhibitors**

Tyrosine kinase inhibitors
- Gefitinib
- Erlotinib

---

**The Pathway From Concept to Clinical Trials**

- The concept:
  - Targeted therapy may have potential with a broad range of common solid tumors.

- Clinical trials:
  - Targeted therapy is well-tolerated.
  - Tumor responses have been seen in several tumor types.

- The promise:
  - Targeted therapies may improve outcomes in the treatment of common solid tumors.
Targeting HER1/EGFR: New Strategies, New Agents

Michael Morse, MD
Associate Professor of Medicine
Clinical Leader, GI Oncology
Duke University Medical Center
Durham, North Carolina

EGFR Signaling

Clinical Breakthroughs in EGFR Inhibition: Applying the Science to Your Clinical Practice
EGFR Pathway Activation

Anti-EGFR Approaches

Clinical Breakthroughs in EGFR Inhibition: Applying the Science to Your Clinical Practice
EGFR Receptor Blockers: Monoclonal Antibodies

- Cetuximab (Erbitux®, ImClone)
  - Chimeric
- Panitumumab (ABX-EGF, Amgen)
  - Fully human
- Matuzumab (EMD 72000, Merck)
  - Humanized

EGFR Receptor Blockers: Tyrosine Kinase Inhibitors

- Erlotinib (Tarceva®, Genentech, OSI)
- Gefitinib (Iressa®, AstraZeneca)
- CI-1033 (Pfizer)
  - pan-Erb B
  - HER1, 2, and 4
- EKB569 (Wyeth)
  - pan-Erb B
  - HER1, EGFR
- Lapatinib (Tykerb, GlaxoSmithKline)
  - EGFR, erbB-2
- ZD6474 (Zactima™, AstraZeneca)
  - EGFR, VEGFR
Cetuximab
FDA-Approved Monoclonal Antibody

- t1/2 114hr
  - Weekly dosing
- Chimeric IgG1 (mouse/human)
  - Allergic reaction possible
- TGF-α
  - Binds better than natural ligand

- No dimerization
- No signal transduction
- Receptor internalization

Chemotherapy or radiation

Apoptosis

Clinical Breakthroughs in EGFR Inhibition

BOND Study:
Cetuximab ± Irinotecan in CRC

- Irinotecan dose and schedule used during progression
  - Cetuximab 400 mg/m² 1st infusion, then 250 mg/m²/week

- Patients with CRC progressed on or within 3 months of irinotecan-based chemotherapy
  - n=218

- Randomization
  - n=111

- Cetuximab 400 mg/m²
  - 1st infusion, then 250 mg/m²/week

- Irinotecan dose and schedule used during progression
  - Cetuximab 400 mg/m²
  - 1st infusion, then 250 mg/m²/week

Schema

Cunningham et al., 2003.

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### BOND Study: Overall Results

<table>
<thead>
<tr>
<th></th>
<th>Irinotecan + Cetuximab</th>
<th>Cetuximab Alone</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (%)</td>
<td>22.9%</td>
<td>10.8%</td>
<td>0.0074</td>
</tr>
<tr>
<td>Dz Control (%)</td>
<td>55.5%</td>
<td>32.4%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median TTP</td>
<td>4.1 months</td>
<td>1.5 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median survival</td>
<td>8.6 mo [7.6-9.6]</td>
<td>6.9 mo [5.6-9.1]</td>
<td>0.48</td>
</tr>
</tbody>
</table>

#### Adverse Events:

<table>
<thead>
<tr>
<th>Event</th>
<th>Irinotecan + Cetuximab</th>
<th>Cetuximab Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>21%</td>
<td>2%</td>
</tr>
<tr>
<td>Rash</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Cunningham et al., 2003.

### Activity of Cetuximab in Other Settings of CRC

<table>
<thead>
<tr>
<th></th>
<th>IFL+ Cetuximab Rosenberg, 2002</th>
<th>FOLFIRI+ Cetuximab Van Laethem, 2003</th>
<th>FOLFOX+ Cetuximab Taberno, 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (%)</td>
<td>48</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>MR/SD (%)</td>
<td>41</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>PD (%)</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
E5397 Study: Cisplatin + Cetuximab in 1st-Line Head and Neck Cancer - Phase III study

**Stratification:**
New diagnosis vs. recurrent
PS 0 vs. 1

**RANDOMIZATION**
Cross-over permitted

<table>
<thead>
<tr>
<th>Cisplatin + Cetuximab</th>
<th>Cisplatin + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>RR</td>
</tr>
<tr>
<td>26%</td>
<td>9.8%</td>
</tr>
<tr>
<td>PFS</td>
<td>PFS</td>
</tr>
<tr>
<td>4.2m</td>
<td>3.4m</td>
</tr>
<tr>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>9.3m</td>
<td>8m</td>
</tr>
</tbody>
</table>

Grade 3/4 tox: Mg 14%, neut 28%, rash 18%, rxn 7%
Grade 3/4 tox: Mg 0%, neut 12%, rash 0%, rxn 2%

Cetuximab + RT for Loco-Regionally Advanced Head and Neck Cancer:
FDA-Approved in March 2006

**Stratification:**
KPS, LN+, T stage, XRT fraction

**RANDOMIZATION**

<table>
<thead>
<tr>
<th>RT + Cetuximab</th>
<th>RT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>54m</td>
<td>28m</td>
</tr>
</tbody>
</table>

Grade 3/4 tox: Mucositis 55%, rash 34%, rxn 3%
Grade 3/4 tox: Mucositis 52%, rash 18%, rxn 0%
Clinical Breakthroughs in EGFR Inhibition: Applying the Science to Your Clinical Practice

Other Cetuximab Clinical Trials

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Phase</th>
<th>Treatment</th>
<th>RR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC, recur</td>
<td>II</td>
<td>docetaxel</td>
<td>22%</td>
<td>2.6 PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kim et al., 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC, Stage III,IV</td>
<td>II</td>
<td>cisplatin, vinorelbine +/- Rosell</td>
<td>59%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>et al., 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC, Stage IV</td>
<td>I/II</td>
<td>carboplatin, paclitaxel</td>
<td>29%</td>
<td>4.5 TTP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kelly et al., 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC, Stage IV</td>
<td>I/II</td>
<td>gemcitabine, carboplatin</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Robert et al., 2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic, Stage IV, locally advanced</td>
<td>II</td>
<td>gemcitabine</td>
<td>12%</td>
<td>1Y:17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xiong et al., 2004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predictors of Clinical Activity: Efficacy and Rash

<table>
<thead>
<tr>
<th>Acne-Like Rash</th>
<th>Irinotecan + Cetuximab</th>
<th>Cetuximab Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response Rate (%)</td>
<td>Survival (Months)</td>
</tr>
<tr>
<td>None</td>
<td>16.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Any</td>
<td>24.7</td>
<td>8.9</td>
</tr>
<tr>
<td>≥ Grade 2</td>
<td>30.9</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Cunningham et al., 2003.
Intensity of EGFR Staining

Does intensity of EGFR staining matter? No.

The primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit.

<table>
<thead>
<tr>
<th>EGFR staining</th>
<th>Cetuximab + irinotecan</th>
<th>Cetuximab monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n ORR (%)</td>
<td>n ORR (%)</td>
</tr>
<tr>
<td>Faint/barely</td>
<td>53 21</td>
<td>21 5</td>
</tr>
<tr>
<td>Weak to moderate</td>
<td>89 25</td>
<td>55 13</td>
</tr>
<tr>
<td>Strong</td>
<td>75 23</td>
<td>34 12</td>
</tr>
</tbody>
</table>

Data on File, ImClone Systems Inc., Bristol-Myers Squibb Company.

---

Intensity of EGFR Staining

- DakoCytomation EGFR pharmDx™ test kit
  - Received FDA approval for cetuximab in EGFR + CRC
- BUT:
  - The intensity of EGFR staining 1%, 1+, 2+, 3+ does not correlate with response rate.
  - Results for EGFR negative patients
    - 16 chemo-refractory CRC patients
    - EGFR negative
    - Irinotecan + cetuximab (14) or cetuximab alone (2)
    - 4 (25% with PR), 2 (12% with MR)

Chung et al., 2005.
EGFR Mutations: No Relevance Has Been Identified to Date.

Lenz, 2004:
- Irinotecan and oxaliplatin refractory patients received cetuximab.
- 12% RR, 43% disease control, 6.7 mo MS
- There was no association of response and EGFR mutation status.
  - All responders had wild-type.
  - The mutations seen in EGFR were not those seen in lung cancer.
  - Of 9 patients with EGFR negative tumors, 1 PR, 3 SD


Erlotinib and Gefitinib
FDA-Approved TKIs

Clinical Breakthroughs in EGFR Inhibition: Applying the Science to Your Clinical Practice
Gefitinib

- Gefitinib (Iressa®, AstraZeneca)
  - Orally available, reversible tyrosine kinase inhibitor
  - May be more effective in patients with particular mutations of the EGFR TK domain
- Gefitinib received FDA accelerated approval (2003) for 3rd-line therapy in patients with advanced NSCLC after failure of both platinum-based and docetaxel chemotherapies.
- Use is restricted to patients who have shown benefit previously or who are on clinical trials (no “new” patients).
- ISEL study:
  - Locally advanced or metastatic NSCLC
  - Failed 1 or 2 prior regimens
  - Randomized to gefitinib 250 mg versus placebo
  - Gefitinib failed to significantly prolong survival.
    - Overall survival 5.6 vs. 5.1 mo (NS)
    - In adenoCa 6.3 vs. 5.4 mo ($P = 0.07$)


Erlotinib

- Erlotinib (Tarceva®, Genentech)
  - Highly selective, potent, and reversible inhibitor of HER1/EGFR-TK phosphorylation
  - Blocks tumor cell proliferation and promotes apoptosis
  - Produces stasis and regression in NSCLC and other human xenografts
  - Orally available, well tolerated

- Erlotinib received FDA approval in November 2004 for advanced NSCLC (2nd- and 3rd-line).

Erlotinib (cont.)

- Erlotinib as single agent (BR.21)
  - Stage IIIB/IV NSCLC, PS 0-3, 1-2 chemotherapy regimens
  - Erlotinib 150 mg po qd vs. placebo
  - RR: 8.9%
  - OS: erlotinib: 6.7 mo vs. 4.7 mo (P = 0.001)
  - PFS: erlotinib: 2.23 mo vs. 1.84 mo (P < 0.001)
  - FDA approval: locally advanced or metastatic NSCLC after failure
    of at least one prior chemotherapy regimen

- Erlotinib in combination:
  - Two multicenter, placebo-controlled, randomized, phase III trials
    conducted in first-line patients with locally advanced or metastatic
    NSCLC
  - No clinical benefit with the concurrent administration of erlotinib
    with platinum-based chemotherapy (carboplatin and paclitaxel or
    gemcitabine and cisplatin)
  - Its use is not recommended in first line with chemotherapy.

Shepherd et al., 2004, Shepherd et al., 2005.
Rash as Predictor of Response

Rash (%)

<table>
<thead>
<tr>
<th>Grade</th>
<th>GO</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>33</td>
<td>38</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Time to first rash: 7-10 days
Day 1 AUC with trend to predict onset of rash ($P = 0.11$)

Bruno et al., 2003; Clark et al., 2003.

Erinotinib/Gefitinib: Other Clinical Trials

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Phase</th>
<th>Treatment</th>
<th>RR</th>
<th>OS/TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic, Stage IV, 1st line</td>
<td>III</td>
<td>gemcitabine + erlotinib vs. gemcitabine alone</td>
<td>9% vs. 8%</td>
<td>6.4 vs. 5.9 OS (significant)</td>
</tr>
<tr>
<td>CRC, Stage IV, 1st line</td>
<td>II</td>
<td>FOLFOX + gefitinib</td>
<td>77%</td>
<td>9.5 TTP</td>
</tr>
<tr>
<td>CRC, Stage IV, 2nd line</td>
<td>II</td>
<td>FOLFOX+ gefitinib</td>
<td>29%</td>
<td>5.2 TTP</td>
</tr>
</tbody>
</table>

Moore et al., 2005; Zampino et al., 2005; Kuo et al., 2005.
Targeting HER1/EGFR: Summary

- Monoclonal antibodies such as cetuximab target EGFR by binding to and inhibiting the function of the receptor.
  - Clinical trials demonstrate activity in colon cancer refractory to standard chemotherapy and in head and neck cancer with radiation and chemotherapy.
  - The rash correlates with clinical activity in some studies. This has not been a uniform finding in clinical trials.

- Tyrosine kinase inhibitors such as gefitinib and erlotinib inhibit the signaling function of the receptor.
  - Clinical trials demonstrate activity of erlotinib as a single agent in refractory NSCLC and with gemcitabine in pancreatic cancer.
  - EGFR mutations may correlate with activity in NSCLC. This has not been a uniform finding in clinical trials.

- New targeted therapies are on the horizon, such as panitumumab, matuzumab, and multi-targeted agents.

Preparing Your Practice: Nursing Implications and Side Effects

Teresa Knoop, MSN, RN, AOCN®
Clinical Nurse Specialist
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee
Side Effects and Nursing Implications Related to Targeting EGFR

- Monoclonal antibodies:
  - Infusion reactions
  - Hypomagnesemia

- Monoclonal antibodies and tyrosine kinase inhibitors:
  - Diarrhea
  - Rash
  - Interstitial lung disease (ILD) - rare

Side Effects Common to EGFR Monoclonal Antibody Therapy: Infusion Reactions

*The biology:*

- Mild to moderate infusion reactions are related to nature of the monoclonal antibody and mediated by release of cytokines (cytokine release syndrome).
- In general, monoclonal antibodies and other biological agents tend to be associated with cytokine release syndrome.
- Some monoclonal antibodies (especially murine and chimeric) are also associated with hypersensitivity reactions.

Side Effects Common to
EGFR Monoclonal Antibody Therapy:
Infusion Reactions (cont.)

The patient:

- Pre-medication may or may not be necessary.
  - Consider the drug used and whether patient has had previous infusion reactions.
- Most reactions are mild to moderate.
  - Chills, fever, dyspnea, rigors, myalgias
- It is important to monitor the patient post-treatment.
  - You may need to monitor the patient for at least one hour after infusion, and you may need to extend that time if infusion reactions are experienced.
    - Cetuximab requires monitoring for a minimum of one hour.

Side Effects Common to
EGFR Monoclonal Antibody Therapy:
Infusion Reactions - Cetuximab

- 90% occur during the first infusion.
- 16%-19% are mild to moderate; 3% are severe (rarely fatal <1 in 1000).
- Severe infusion reaction:
  - Airway obstruction with bronchospasm, stridor, and hoarseness
  - Hypotension, Urticaria
- Observe the patient for one hour following infusion, and longer if the patient experiences infusion reactions.

Other side effects seen with cetuximab + RT (Head/neck cancer)
- Heart attack or sudden death (2%); lung disease (rare)
- Mouth sores (6%), skin irritation (3%), confusion (2%), diarrhea (2%)
- Late radiation side effects
  - Mouth, voice box, food pipe, skin, brain, lung, spinal cord and bone
Side Effects Common to EGFR Monoclonal Antibody Therapy: Infusion Reaction Management

**Clinical practice:**
- Stop the infusion.
- Maintain an infusion line.
- Assess the patient for respiratory or cardiac compromise.
- Keep an emergency cart and medications nearby.
- If you are restarting the drug after a mild to moderate infusion reaction, pre-medicate and use a slow infusion.
- For severe reactions, permanently discontinue the drug.

---

Side Effects Common to EGFR Monoclonal Antibody Therapy: Infusion Reaction Management (cont.)

- **Anaphylaxis**
  - Epinephrine 0.1 to 0.5 mL sub q
  - Diphenhydramine 25 to 50 mg IVP
  - Hydrocortisone 50 to 100 mg IVP
  - Oxygen

- **Wheezing, hypotension**
  - Albuterol nebulizer
  - Sodium chloride 0.9% 250 mL IV
Side Effects Common to EGFR Monoclonal Antibody Therapy: Hypomagnesemia

The biology:

- The hypothesis is that EGFR is strongly expressed in the kidney, where most of magnesium is reabsorbed into the organ.
  - Blocking EGFR may interfere with magnesium transport.

- The product insert for cetuximab recently has been changed.
  - In a study of 244 patients, 50% had hypomagnesemia.
  - 10%-15% of the cases were severe.

- Hypomagnesemia is being monitored in clinical trials for other EGFR monoclonal antibodies.

Side Effects Common to EGFR Monoclonal Antibody Therapy: Hypomagnesemia (cont.)

The patient:

- Symptoms of hypomagnesemia include:
  - Fatigue
  - Paresthesias

- May be associated with hypocalcemia and hypokalemia

- Patients may need magnesium supplementation.
  - If the hypomagnesemia is severe, patients may need IV supplementation.

- Patients may also need other electrolyte supplementation.
Side Effects Common to EGFR Monoclonal Antibody Therapy: Hypomagnesemia (cont.)

Clinical Practice:
• Hypomagnesemia may occur any time from days to months after the initiation of the drug.
• Monitor magnesium, calcium, and potassium levels.
• The time to resolution of electrolyte abnormalities is not well known.
  – Recommendation: Continue to monitor after the treatment is discontinued (based on half-life of product).

Side Effects Common to EGFR Inhibitors: Monoclonal Antibodies and Tyrosine Kinase Inhibitors

• Side effects that are common to EGFR inhibitors include:
  - Diarrhea
  - Rash
  - Interstitial lung disease (ILD) - rare
Side Effects Common to EGFR Inhibitors: 
Diarrhea

The biology:
- EGFR is expressed in the epithelial tissue of the GI tract.

The patient:
- While common, diarrhea is generally mild to moderate and can be well controlled.
  - Diarrhea is rarely severe/uncontrolled.
- If diarrhea is severe and unresponsive to anti-diarrheal therapy, the EGFR inhibitor may need to be dose-reduced or interrupted.

Clinical practice:
- Loperamide
  - 4 mg after first stool
  - 2 mg after every subsequent stool
- Add diphenoxylate hydrochloride/atropine sulfate.
  - Lomotil®, Pfizer
  - 2.5 to 5 mg qid
- Proactive patient management is important.
- Provide specific patient instructions regarding when the doctor or nurse should be notified.
- Patients should be advised to maximize fluid intake and modify diet.
Side Effects Common to EGFR Inhibitors: Interstitial Lung Disease (ILD)

- ILD has been observed at a relatively low rate.
  - However, ILD is a very serious condition that can lead to fatality.
- Patients should be carefully monitored for signs and symptoms of ILD.
  - Hold doses until ILD can be ruled out; if ILD is confirmed, discontinue drug.
- Treatment:
  - High dose corticosteroids, oxygen therapy, possible hospitalization.

AstraZeneca, 2005; Genentech, 2005.

Side Effects Common to EGFR Inhibitors: Skin Rash

- Rash is the most distinctive side effect of treatments targeting EGF and EGFR.
- Skin rash has been associated with response in multiple studies (data is not conclusive).

Example:

<table>
<thead>
<tr>
<th>Muhamed et al., 2004</th>
<th>Median Survival</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with rash of any grade</td>
<td>11 months</td>
<td>$P = 0.0001$</td>
</tr>
<tr>
<td>Patients without rash</td>
<td>4.5 months</td>
<td></td>
</tr>
</tbody>
</table>

Hotta et al., 2004; Spaeth et al., 2004; Muhamed et al., 2004; Hidalgo, 2001; Perez-Soler et al., 2005.
Clinical Discussion:
Managing the EGFR-Inhibitor Rash

Leslie Tyson, MS, APRN-BC, OCN®
Nurse Practitioner, Thoracic Oncology Service
Memorial Sloan-Kettering Cancer Center
New York, New York

EGFR-TKIs: Skin Effects

- Skin rash
  - Pustular rash
- Other skin effects
  - Dry skin
  - Erythema
  - Pruritis
  - Fissures
  - Nail and cuticle cracking
  - Vaginal dryness
  - Abnormal hair growth
Skin Rash: Terminology

- Typical descriptions of HER1/EGFR inhibitor rash include:
  - Acne, acneiform skin reaction, acneform rash, acneform follicular rash, acne-like rash, maculopapular skin rash, and monomorphic pustular lesions.
- The rash does not appear to have similar histology to acne and should not be described as acne, acneiform, or acne-like.
- The rash may be a new dermatologic entity.
- The rash should be characterized in phenotypic terms.
  - Pustular/papular rash
  - Pustular eruption
  - Follicular/intrafollicular pustular eruptions

Perez-Soler et al., 2005.

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Skin Rash: Common Toxicity Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Macular or papular eruption or erythema without associated symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Macular or papular eruption or erythema with pruritus or other associated symptoms, or localized desquamation, covering &lt; 50% of body surface area</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic generalized erythroderma or macular, papular, or vesicular eruption or desquamation covering ≥ 50% of body surface area</td>
</tr>
<tr>
<td>4</td>
<td>Generalized exfoliative dermatitis or ulcerative dermatitis</td>
</tr>
</tbody>
</table>

EGFR Inhibitor-Induced Rash

Facts
- Rash is a common side-effect of all EGFR-targeted agents.
- The rash is mostly mild to moderate.
- The etiology of the rash is unclear.
- Data are inconclusive regarding the correlation between the rash and clinical outcomes.
- Evidence-based treatment recommendations are not available.

The biology:
- The nature of this rash is papular/pustular adenitis (PPA) associated with HER1/EGFR inhibitor treatment.
- The rash is an inflammatory reaction.
- It is mediated by neutrophils and inflammatory CD11c+ myeloid cells.
  - It is not an allergic reaction.
- The mechanism of this toxicity is not fully understood.

Genentech, clinical trial data on file, 2004; Hidalgo, 2001; Perez-Soler et al., 2005.
EGFR Inhibitor-Induced Rash (cont.)

The patient:

- The onset of rash is usually observed within the first two weeks of dosing.
- An improvement in rash severity is usually observed with continuation of dosing.
  - Occasionally, rash develops late in the therapeutic course.
- The rash typically has an “above-waist” distribution and includes the face, scalp, neck, arms, chest, and back.

Genentech, clinical trial data on file, 2004; Hidalgo, 2001; Perez-Soler et al., 2005.

Rash Management:
Patient Information

- Makeup:
  - Use a dermatologist-approved cover-up such as Dermablend®.
- Cleanser:
  - Use liquid cleansers such as Neutrogena®, Dove®, and Ivory® soap.
- Moisturizer:
  - Use moisturizers such as Curel®, Eucerin®, Neutrogena®, and Vaseline Intensive Care®.
- Use sun protection.
- Over-the-counter medications
Rash Management: Medications

Clinical practice:

- Recommended:
  - Analgesics
    - Can be used for painful rash
  - Anti-itch medications
  - Antibiotics
    - Topical or short-course antibiotics can be used to treat infection.
  - Over-the-counter medications

Perez-Soler et al., 2005.

Rash Management: Medications (cont.)

- Not recommended:
  - Corticosteroids
    - Have been used topically in early stage rash
    - Not recommended in severe rash
  - Immunomodulatory agents
    - Unknown effects on the tumor
  - Retinoids
    - Can dry skin and exacerbate the rash

Perez-Soler et al., 2005.
Rash Management:
Other

- Provide education and support for staff and patients.
- Provide a dermatology referral.
- Discuss dose reduction, interruption, or cessation.
- Patients should not stop using the drug without a physician consultation.

EGFR Inhibitors: Skin Effects

- Dry Skin:
  - Use lotions and emollients.
  - Avoid products with alpha hydroxy acid.
- Pruritis:
  - Use lotions and emollients.
  - Avoid products with alpha hydroxy acid.
  - Use diphenhydramine or hydroxyzine as needed.
EGFR Inhibitors: Skin Effects (cont.)

- Vaginal Dryness:
  - Use a water-based lubricant.
- Skin Cracks (fissures):
  - Use moisturizers, cotton gloves and socks, and Bag Balm®.
- Photosensitivity:
  - Use a sunscreen such as Anti Helios®.

Future Directions: Targeting EGFR
New EGFR Inhibitors in Development

Michael Morse, MD
Associate Professor of Medicine
GI Oncology
Duke University Medical Center
Panitumumab (ABX-EGF, Amgen)

- Fully human IgG2 monoclonal antibody targeting EGFR
- Allergic reactions and infusion reactions are rare.
- Flexible dosing may be possible.
  - 6 mg/kg q 2 weeks and 9 mg/kg q 3 weeks have similar exposure and tolerability.
  - 2.5 mg/kg/week
- Phase II study:
  - 1st-line metastatic CRC
- Phase III study (Pivotal Trial)
  - FDA fast-track designation for 3rd-line metastatic CRC
- Phase III study:
  - 1st-line metastatic CRC; initiated April 2005

Avends et al., 2005; Malik et al., 2005; Weiner et al., 2005.
Other Panitumumab Clinical Trials

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Phase</th>
<th>Treatment + Panitumumab</th>
<th>RR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC, Stage IIIB, IV</td>
<td>I, II</td>
<td>Carboplatin paclitaxel</td>
<td>26%</td>
<td>N/S</td>
</tr>
<tr>
<td>NSCLC, Stage IIIB, IV</td>
<td>*Results updated at the European Cancer Conference (ECCO). Crawford et al., 2005.</td>
<td>15% vs. 11% carboplatin/paclitaxel</td>
<td>8.5 mo. vs. 8 mo. carboplatin/paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Renal Cell</td>
<td>I</td>
<td>Panitumumab alone</td>
<td>3.5%</td>
<td>100 days PFS</td>
</tr>
</tbody>
</table>

Crawford et al., 2004; Crawford et al., 2005; Rowinsky et al., 2004.

Panitumumab: Metastatic CRC
Phase III Study - Interim Results (April 3, 2006)

- Criteria:
  - Metastatic CRC
  - Patients with mCRC who had failed standard chemotherapy

- N = 463
  - Panitumumab + BSC = 231
  - BSC = 232

- Dosage:
  - Panitumumab administered once every 2 weeks at 6 mg/kg intravenously with no loading dose

- Endpoints:
  - Primary endpoint: Progression-free survival (PFS)
  - Secondary endpoints: Objective response (OR) and overall survival (OS)

AACR, 2006.
Clinical Breakthroughs in EGFR Inhibition

Panitumumab: Metastatic CRC (cont.)
Phase III Study - Interim Results (April 3, 2006)

- Primary endpoint:
  – 46% decrease in tumor progression rate vs. best supportive care (BSC)
    - $P < 0.000000001$
    - Exceeded the pre-specified measure of 33% decrease in tumor progression rate vs. best supportive care
- Disease control = 36% vs. 10% (BSC), as shown by response rate and stable disease.
  – Response rate = 8% vs. 0% (BSC)
    - Median duration of response = 17 weeks
  – Stable disease rate = 28% vs. 10% (BSC)
- Overall survival between the two groups was similar.

AACR, 2006.

Panitumumab: Metastatic CRC (cont.)
Phase III Study - Interim Results (April 3, 2006)

- Cross-over arm (n = 174)
  – 75% of BSC patients entered a cross-over arm to receive panitumumab after disease progression
    - Partial response = 9%
    - Stable disease = 32%
- Safety analysis:
  - Incidence of infusion reactions of any severity was low (no Grade 3 or 4).
  - Adverse events were consistent with previous studies of panitumumab.
    – Skin toxicity, fatigue, abdominal pain, nausea, and diarrhea.
  - Hypomagnesemia was observed in 38% of patients (3% Grade 3 or 4).

AACR, 2006.
Panitumumab: CRC Phase III Study (on-going)

- 1st line metastatic CRC; initiated April 2005
- Panitumumab Advanced Colorectal Cancer Evaluation (PACCE)
- Randomized, multi-center, open-label study

Matuzumab (EMD 72000, Merck)

- Humanized monoclonal antibody against EGFR
- TGF-α
- Matuzumab
- Chemotherapy or radiation
- No dimerization
- No signal transduction
- Receptor internalization
- Apoptosis
Matuzumab

- Humanized monoclonal antibody that targets EGFR
- Phase I trial:
  - 22 patients with EGFR+ tumors (15 colon)
    - Median of 3 prior chemotherapy
  - Doses of 1,200 mg every 1, 2, or 3 weeks
  - No grade 3-4 toxicities were observed.
  - 2 PR, 1 MR, 1 SD (6+ m) in patients with colon cancer
- Responses observed at the 3 different schedules:
  - Complete inhibition of pEGFR & pMAPK
  - Decrease in Ki67 and an increase in p27 in skin samples
  - Tumor pEGFR & pMAPK was inhibited in all patients

Vanhoef et al., 2004.

Clinical Breakthroughs in EGFR Inhibition

Applying the Science to Your Clinical Practice

Matuzumab: Phase II Study
Ovarian Cancer

- Multi-center, open-labeled trial
- Criteria:
  - Women with a history of platinum-resistant ovarian cancer or primary peritoneal carcinoma (median of 7 lines of prior therapy)
- Dosage:
  - 800 mg matuzumab weekly with reassessment every 8 weeks
- Results:
  - Matuzumab was well tolerated.
  - Common toxicities included skin toxicities, headache, dizziness, fatigue, and diarrhea.
  - Serious adverse events were rare (1 instance of pancreatitis).
  - No formal responses, but 21% of patients stayed on therapy more than 6 months with stable disease.

Vanhoef et al., 2004.
Lapatinib – Phase III Study: Interim Results
Refractory Advanced or Metastatic Breast Cancer

- Phase III Study:
  - Lapatinib in combination with capecitabine vs. capecitabine alone
- Criteria:
  - Women with refractory advanced or metastatic breast cancer
    - ErbB2 (HER2) overexpression
    - Disease progression following treatment with trastuzumab (Herceptin®, Genentech), or other therapies
- N = 321 patients
  - Combination arm = 160
  - Monotherapy arm = 161
- The primary endpoint of the study was to detect a 50% increase in time to disease progression (TTP) in the combination arm.
- Results:
  - Enrollment was halted in the study because the interim analysis showed that the study had exceeded its primary endpoint of TTP.

GlaxoSmithKline, 2006.
Combining Targeted Agents

- **t1/2 114hr** Weekly dosing
- **Chimeric IgG1 (mouse/human)** Allergic reaction possible
- **TGF-α**
- **Cetuximab** Binds better than natural ligand
- **Bevacizumab**
- **VEGF**
- No dimerization
- No signal transduction
- Receptor internalization
- Apoptosis
- No secretion of VEGF

Anti-Angiogenic Therapy + Anti-EGFR Therapy: Bevacizumab + Cetuximab

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11 + bevacizumab + cetuximab</td>
<td>38%</td>
<td>8.5 mo</td>
</tr>
<tr>
<td>MCRC bevacizumab + cetuximab</td>
<td>23%</td>
<td>6.9 mo</td>
</tr>
</tbody>
</table>

Saltz et al., 2005.
Multi-Targeted Agents

- ZD6474: Inhibits VEGFR2, EGFR, and RET
- Lapatinib: Inhibits EGFR and HER2
- CI-1033: Inhibits EGFR and HER2
- EKB-569: Irreversibly inhibits EGFR and HER2
  - Inhibits the gefitinib- and erlotinib-resistant EGFR(L858R/T790M) kinase

Summary

- Targeting EGFR alone has activity, but targeting more than one pathway is likely to be necessary.
- Targeting EGFR and VEGF pathways is synergistic.
- Multi-targeted tyrosine kinase inhibitors are an exciting new direction under development.
Clinical Breakthroughs in EGFR Inhibition: Applying the Science to Your Clinical Practice


Applying the Science to Your Clinical Practice

**Clinical Breakthroughs in EGFR Inhibition: Applying the Science to Your Clinical Practice**


**Glossary**

**adenocarcinoma** – a type of carcinoma arising from gland cells

**adenosine Triphosphate (ATP)** – nucleotide within the cell participates in many signaling functions. The energy currency or coin of the cell; transfers energy from chemical bonds to endergonic (energy absorbing) reactions within the cell

**angiogenesis** – development of new capillaries, resulting in increased tissue

**apoptosis** – programmed cell death; through a highly regulated normal physiologic process, damaged or excess cells are fragmented into membrane-bound particles, which are ingested by phagocytic cells.

**autocrine** – a hormone or protein; acts on the same cell that produced it

**bAX protein** – plasma membrane protein; pro-apoptotic

**Bcl-2** – the prototype for a family of genes that can be either pro-apoptotic (Bax, Bak, and Bok among others) or anti-apoptotic (including Bcl-2, Bcl-xL, Bcl-w, etc.). May activate or inactivate inner mitochondrial permeability transition (PT) pore, which is involved in the regulation of matrix Ca$^{2+}$, pH, and voltage. It is also thought that some Bcl-2 family proteins can induce (pro-apoptotic members) or inhibit (anti-apoptotic members) the release of cytochrome c into the cytosol that activates caspase-9 and caspase-3, leading to apoptosis.

**caspase** – a type of protein that is involved in apoptosis. Caspases are characterized by their unusual ability to cleave proteins at specific sites. Caspases can often activate other caspases, leading to a cascade of protein degradation.

**cell-signaling cascades** – groups of factors that are linked and pass on messages from the cell surface to the inside of the cell

**chimeric antibody** – an antibody that is made of both mouse and human antibodies, usually a 30/70 percent split, respectively

**compartment pharmacokinetic models** – mathematical approaches to calculating dosing regimens or predicting serum concentrations. Which model to use is determined from the experimental data. Pharmacokinetics refers to the processes of the uptake of drugs by the body, the biotransformations they undergo, and how the parent drug and its metabolites are distributed within and eliminated from the body. These processes may change in a dose-dependent manner.

**cyclin D1** – cell cycle control protein involved in signal transduction and cell communication; stimulated by epidermal growth factor; implicated in colorectal cancer

**dimerization** – process triggered by a single ligand binding to two cell surface receptors. It can occur between two identical receptors (homodimerization) or between different members of the same receptor family (heterodimerization).

**downregulation** – reduced expression. With cell surface receptors, this may occur naturally as a regulatory mechanism via ligand binding or genetic events that decrease receptor expression. Failure of a cell to downregulate receptor expression may occur in cancer cells.
**dysregulation** – overproduction or underproduction of growth factors

**ECOG** – The Eastern Cooperative Oncology Group (ECOG) is one of the largest clinical cancer research organizations in the United States and conducts clinical trials in all types of adult cancers.

**endothelial cells** – mesodermal-derived cells that line the lumen of blood vessels, lymph vessels, the cavities of the heart, and the serous cavities of the body

**epidermal growth factor (EGF)** – a growth factor that is important in the development of the cells. It binds to a receptor on the cell surface called the epidermal growth factor receptor (EGFR) to create a growth signal.

**epidermal growth factor receptor (EGFR)** – Epidermal growth factor receptor is a member of a family of four receptors (EGFR [HER1 or ErbB1], ErbB2 [HER2/neu], ErbB3 [HER3], and ErbB4 [HER4]). These receptors are large proteins that reside in the cell membrane, and each has a specific external ligand-binding domain, a transmembrane domain, and an internal domain that has tyrosine kinase enzyme activity.

**ErbB2 oncoprotein** – also known as HER2/neu; part of the EGFR family of proteins, frequently overexpressed in cancers (breast, lung)

**first-line treatment** – the initial treatment given for cancer. It is usually the treatment that is widely recognized to be the most effective for that tumor type.

**growth factor** – a substance that promotes the growth of cells. Growth factors include epidermal growth factor (EGF), fibroblast growth factor (FGF), erythropoietin (EPO), hematopoietic cell growth factor (HCGF), platelet-derived growth factor (PDGF), stem cell factors, and neurotrophins.

**hazard ratio** – estimated relative risk of the event of interest occurring in a group

**heterodimer** – union of two similar but not identical monomers

**homeostasis** – sustained equilibrium

**homodimer** – union of two identical monomers

**humanized antibody** – an antibody that contains more than 90% human material

**kinases** – enzymes that transfer a phosphate group from one molecule to another. Involved in intracellular signaling.

**K-ras** – The ras family of oncogenes is constituted of three principal members (K-ras, H-ras and N-ras) all of which have been implicated in the development of human malignancies. The K-ras oncogene resides on chromosome 12p12 and encodes a 21-kD protein (p21ras) involved in the G-protein signal transduction pathway, modulating cellular proliferation and differentiation.

**ligand** – the agent that binds to and activates a receptor

**matrix metalloproteinases (MMPS)** – The MMP family of enzymes contributes to both normal and pathologic tissue remodeling. MMPs play a key role in the migration of normal and malignant cells through the body. They also act as regulatory molecules, both by functioning in enzyme cascades and by processing matrix proteins, cytokines, growth factors, and adhesion molecules to generate fragments with enhanced or reduced biologic effects.

**monoclonal antibodies** – produced by a single clone of hybridoma cells and therefore a single species of antibody molecule

**monomer** – molecule of protein

**neoadjuvant therapy** – therapy (chemo-, radio-, or hormonal therapy) that is given to a tumor before surgery. Its purpose is to reduce tumor size to aid the surgical procedure and also to kill any cells that might be shed during the operation.

**oncogenes** – a gene having the potential to cause a normal cell to become cancerous
**p53** – The tumor suppressor gene *p53* is located at chromosome region 17p13 and is one of the most frequently mutated genes in human cancers. The normal function of *p53* includes regulation of critical cellular functions involving the G1 and G2 cell-cycle checkpoints in response to DNA damage and apoptosis induced by certain stimuli, such as DNA-damaging agents and hypoxia.

**palliative** – treatment that has no curative intent but is given to maintain quality of life and to relieve suffering in a terminally ill patient

**paracrine** – a hormone or protein that acts locally by diffusing from its source to nearby target cells

**performance status** – the level at which a patient is able to perform the routine activities of daily life. Categories of performance have been defined by ECOG, with scores ranging from 1-5 (excellent to dead), and this system is widely applied. Higher scores (3-4) generally suggest that a patient is bedridden and/or unable to care for him/herself.

**phosphorylation** – Protein phosphorylation is an important event through which cellular mechanisms are regulated. Protein phosphorylation reactions are regulated by specific kinases. Cellular phosphorylation cycles are regulated by extracellular signals, cell cycle check points, and environmental stresses. Many of the protein kinases are themselves activated by phosphorylation; this occurs through autophosphorylation or phosphorylation by upstream protein kinases. Therefore, measurement of phosphorylation provides useful information about the activity of specific kinases.

**p-value** – the probability that a variable would assume a value greater than or equal to the observed value strictly by chance

**receptor** – a specialized structure that binds to a ligand to initiate a biologic response. Receptors can be activated by hormones, growth factors, neurotransmitters, and other cellular regulators.

**second-line treatment** – treatment given when first-line treatment has failed

**signal transduction** – the biochemical events that conduct the signal of a hormone or growth factor from the cell exterior, through the cell membrane, and into the cytoplasm. This involves a number of molecules, including receptors, proteins, and messengers.

**signal transduction pathway** – cascade of intracellular reactions that transmit signals from the cell surface to response elements within the cell; the cascade is triggered when an extracellular ligand activates or stimulates the receptor. The response elements usually involve initiation of gene transcription for proteins that control the cell cycle, regulate cell death, change cytoskeletal organization for migration, induce metabolic changes, and produce other mediators such as proteolytic enzymes.

**stroma** – the spongy, colorless framework of a cell

**targeted therapy** – the use of an anticancer agent to block a specific cellular cycle or pathway with the goal of preventing replication or invasion. The use of targeted therapy increases cell kill rates while preserving normal cells through reduced toxicity.

**tumor suppressor genes** – genes with the normal function of regulating and inhibiting inappropriate cellular growth and proliferation. Examples of tumor suppressor genes include von Hippel-Lindau gene, PTEN, and *p53*.

**tyrosine kinase** – also called protein tyrosine kinase; it catalyzes the transfer of a phosphate group from ATP to tyrosine on a substrate protein. A receptor tyrosine kinase contains both an extracellular ligand-binding region and an intracellular tyrosine kinase activated by ligand binding.

**tyrosine kinase inhibitor (TKI)** – small molecule that prevents the phosphorylation of tyrosine kinase and thus prevents signal transduction within a cell. TKIs operate in the intracellular domain.

**upregulation** – increased production or expression of a protein, such as a ligand or a receptor

**vascular endothelial growth factor (VEGF)** – major growth factor involved in stimulation of angiogenesis. Production of VEGF by tumor cells is believed to be the principal, although not the sole, means through which tumor cells induce the proliferations of endothelial cells and formation of the neovasculature required for continued tumor growth. The VEGF family consists of five molecules, designated as A, B, C, D, and E, and the placenta growth factor.
Commonly Used Drug Names and Manufacturers

- Bevacizumab (Avastin®, Genentech BioOncology, San Francisco, CA)
- Carboplatin (Paraplatin®, Bristol-Myers Squibb, Princeton, NJ)
- Cetuximab (Erbitux®, ImClone Systems, Inc., Branchburg, NJ)
- Cisplatin (Platinol®, Bristol-Myers Squibb, Princeton, NJ)
- CI-1033 (in development, Pfizer, Inc., New York, NY)
- Docetaxel (Taxotere®, Aventis, Bridgewater, NJ)
- EKB569 (in development, Wyeth, Collegeville, PA)
- Erlotinib (Tarceva®, Genentech BioOncology, OSI Pharmaceuticals, San Francisco, CA)
- Gefitinib (Iressa®, AstraZeneca, Wilmington, DE)
- Gemcitabine (Gemzar®, Eli Lilly and Co., Indianapolis, IN)
- Irinotecan (Camptosar®, Pfizer, Inc., New York, NY)
- Lapatinib (Tykerb, GlaxoSmithKine, Research Triangle Park, NC)
- Matuzumab (EMD 72000, Merck & Co., Inc. Whitehouse Station, NJ)
- Oxaliplatin (Eloxatin®, Sanofi Aventis, Bridgewater, NJ)
- Paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, NJ)
- Panitumumab (ABX-EGF, Amgen, Thousand Oaks, CA)
- Vinorelbine (Navelbine®, GlaxoSmithKline, Research Triangle Park, NC)
- ZD6474 (Zactima™, AstraZeneca, Wilmington, DE)
How many years of oncology nursing experience do you have? _____________

1. Are you an ONS member?
   a. Yes (if yes, proceed to question 6)
   b. No

2. Primary Position (select one)
   a. Academic Educator
   b. Case Manager
   c. Clinical Nurse Specialist
   d. Consultant
   e. Clinical Trials Nurse
   f. Director/Assistant Director/VP
   g. Genetic Counselor
   h. Nurse Manager/Coordinator
   i. Nurse Practitioner
   j. Patient Educator
   k. Pharmaceutical Representative
   l. Researcher/Principal Investigator
   m. Staff Development
   n. Staff Nurse
   o. Other __________

3. Primary Work Setting
   Inpatient
   a. Bone Marrow Transplant Unit
   b. Intensive Care Unit
   c. Medical/Surgical Unit – General
   d. Medical/Surgical Unit – Oncology
   e. Oncology Specialty Unit
   f. Other __________

   Outpatient
   a. Home Care
   b. Hospice
   c. Hospital-Based Clinic
   d. Physician Office
   e. Radiation
   f. Other __________

   Other
   a. Corporate/Industry
   b. Extended-Care Facility
   c. HMO/Managed Care
   d. School of Nursing
   e. Self-Employed
   f. Other __________

4. Primary Specialty
   a. Biotherapy/Chemotherapy
   b. Bone Marrow Transplant
   c. Palliative Care
   d. Prevention/Detection
   e. Radiation Oncology
   f. Surgical Oncology
   g. Other __________

5. What is the percentage of patients you care for who have an oncology diagnosis?
   a. 0%  d. 75%
   b. 25%  e. 100%
   c. 50%

6. What types of cancers/disorders do you work with most frequently?
   - Breast Cancer
   - Brain Cancer
   - Colon and Rectum Cancer
   - Head and Neck Cancers
   - Hematologic Disorders
   - HIV/AIDS
   - Leukemia
   - Lung and Bronchus Cancer
   - Melanoma
   - Non-Hodgkins lymphoma
   - Prostate Cancer
   - Urinary/Bladder Cancer
   - Other __________

7. To what degree did you achieve the goal of this activity?
   1 = Not at all
   2 = Low
   3 = Medium
   4 = High

The following questions relate to your satisfaction with today’s program. Please use a 1-4 evaluation scale, defined as:

The goal of this program is to educate oncology nurses about how to improve patient outcomes through risk management and on-time interventions for chemotherapy-induced anemia.

(continued on back)
8. To what degree did you achieve the following objectives?
   Objective 1: Discuss the implications of downregulating HER1/EGFR.
   1 2 3 4
   Objective 2: Summarize the therapeutic strategies for targeting HER1/EGFR.
   1 2 3 4
   Objective 3: Identify strategies to prepare your practice to administer HER1/EGFR inhibitors.
   1 2 3 4
   Objective 4: Summarize best practices for managing symptoms related to HER1/EGFR inhibitors.
   1 2 3 4

9. Rate the teaching effectiveness of each speaker:
   **Speaker 1: Teresa Knoop, MSN, RN, AOCN®**
   Presentation delivery
   1 2 3 4
   Reference to current evidence and application to practice
   1 2 3 4
   **Speaker 2: Michael Morse, MD**
   Presentation delivery
   1 2 3 4
   Reference to current evidence and application to practice
   1 2 3 4
   **Speaker 3: Leslie Tyson, MS, APRN-BC, OCN®**
   Presentation delivery
   1 2 3 4
   Reference to current evidence and application to practice
   1 2 3 4

10. Was this educational activity free of commercial bias?
    ❑ Yes ❑ No
    If no, why? _______________________________________________________

11. To what extent do you agree that this program was presented at a level appropriate to your knowledge and experience?
    1 2 3 4

12. What is the primary reason you participated in this CE activity?
    a. I need CE credit for licensure.
    b. I need CE credit for ONC-PRO.
    c. The topic is important to me.
    d. The speakers are well-known.
    e. Other _____________________

13. How will you modify your practice as a result of this program? (check all that apply)
    ❑ Improve skills for patient counseling
    ❑ Improve skills for discussing treatment options with patients
    ❑ Enhance ability to discuss treatment options with multi-disciplinary care team
    ❑ Enhance ability to educate colleagues
    ❑ Improve ability to apply evidence to patient care
    ❑ Other _____________________

14. Which of the following topics do you consider to be your educational priorities? (choose up to 3)
    ❑ Chemotherapy
    ❑ Targeted agents
    ❑ Radiation therapy
    ❑ Safe handling
    ❑ Hematologic toxicities
    ❑ Oral mucositis
    ❑ Nutrition in cancer
    ❑ Chemotherapy-induced nausea and vomiting
    ❑ Breast cancer
    ❑ Colorectal cancer
    ❑ Prostate cancer
    ❑ Leukemias/lymphomas
    ❑ Head and neck cancer
    ❑ Lung cancer
    ❑ Gynecologic cancer
    ❑ Brain cancer
    ❑ Head and neck cancer
    ❑ Urinary/bladder cancer
    ❑ Pancreatic cancer
    ❑ Pain management
    ❑ Skin cancer
    ❑ Genetics
    ❑ Infusion reactions
    ❑ End of life
    ❑ Vascular access devices
    ❑ Geriatric oncology
    ❑ Prevention/early detection
    ❑ Leadership development
    ❑ Complementary & alternative medicine
    ❑ Interpreting data to apply to practice
    ❑ Survivorship
    ❑ Stress management for healthcare professionals
    ❑ Other _____________________

15. How did you learn about this CE program?
    a. Direct mail to home or office
    b. ONS Web site
    c. OES Web site
    d. CJON
    e. ONF
    f. ONS News
    g. ONS e-News
    h. OES Ancillary e-Vents or e-mail announcement
    i. A colleague or friend
    j. Flyer received onsite at IOL
    k. Other – please list: _______________________________

Comments on things we have done well and opportunities for further development:

________________________________________________________________________
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