Epidermal Growth Factor Receptor (EGFR) Mutation Testing for Patients with Advanced Non-Small Cell Lung Cancer Considering First-Line EGFR Tyrosine-Kinase Inhibitor Therapy
The Provisional Clinical Opinion

• “Based on the results of five phase III RCTs, patients with advanced non-small cell lung cancer of the lung who are being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for EGFR mutations to determine which is an appropriate first-line therapy: an EGFR TKI or chemotherapy.”
INTRODUCTION

• The American Society of Clinical Oncology (ASCO) has established a rigorous, evidence-based approach—the provisional clinical opinion (PCO)—to offer a rapid response to emerging data in clinical oncology.

• The PCO is intended to offer timely clinical direction to ASCO members following publication or presentation of potentially practice-changing data from major studies.

www.asco.org/pco/egfr ©American Society of Clinical Oncology 2011. All rights reserved - <released 04/11/11>
INTRODUCTION

• This PCO addresses the clinical utility of epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small cell lung cancer (NSCLC) to predict response to first-line therapy with EGFR tyrosine kinase inhibitors (TKIs; erlotinib or gefitinib)
Statement of the Clinical Issue

• In the United States, approximately 15% of patients with adenocarcinoma of the lung harbor activating *EGFR* mutations. The majority of these mutations are in exons 19 and 21 of the *EGFR* gene.
Statement of the Clinical Issue

• Phase III randomized controlled trials (RCTs) of EGFR tyrosine kinase inhibitors in the first-line setting have shown a benefit in response and progression-free survival (PFS), but not overall survival (OS), for patients with EGFR-mutated NSCLC who received an EGFR TKI in first-line treatment.
Statement of the Clinical Issue

- Greater than 90% of patients included in the majority of these trials had adenocarcinoma of the lung. Currently, neither erlotinib nor gefitinib has been approved for first-line therapy of lung cancer by the US Food and Drug Administration (FDA).
Literature Review and Analysis

- This PCO addresses using epidermal *EGFR* mutation testing in the context of first-line treatment of NSCLC based on trials comparing an *EGFR* TKI to a platinum-based chemotherapy doublet.
- Studies considered were limited to those comparing an *EGFR* TKI to chemotherapy, as the latter has been the standard of care for first-line treatment. The PCO addresses the role of *EGFR* mutation testing in selecting first-line treatment.
### PFS outcomes – included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>EGFR mutation test positive – months</th>
<th>HR (95% CI)</th>
<th>EGFR mutation test negative – months</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPASS</strong></td>
<td>gefitinib</td>
<td>9.5 vs. 6.3</td>
<td>0.48 (0.36-0.64)*</td>
<td>1.5 vs. 5.5</td>
<td>2.85 (2.05-3.98)*</td>
</tr>
<tr>
<td>NEJM 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annals Onc suppl 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JCO suppl 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lee et al.</strong></td>
<td>gefitinib</td>
<td>8.4 vs. 6.7</td>
<td>0.61 (0.31-1.22)</td>
<td>2.1 vs. 6.4</td>
<td>1.52 (0.88-2.62)</td>
</tr>
<tr>
<td>13th WCLC 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maemondo et al.</strong></td>
<td>gefitinib</td>
<td>10.8 vs. 5.4</td>
<td>0.30 (0.22-0.41)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>NEJM 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mitsudomi et al.</strong></td>
<td>gefitinib</td>
<td>9.2 vs. 6.3</td>
<td>0.49 (0.34-0.71)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lancet Onc 2009</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zhou et al.</strong></td>
<td>erlotinib</td>
<td>13.1 vs. 4.6</td>
<td>0.16 (0.10-0.26)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Annals Onc suppl 2010</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: outcomes in bold reached statistical significance

* treatment by biomarker status interaction test p<0.001

www.asco.org/pco/egfr ©American Society of Clinical Oncology 2011. All rights reserved - <released 04/11/11>
The major impetus for the PCO was the publication by Mok et al. that reported the results of the Iressa Pan-Asia Study, or IPASS (NEJM 2009). ASCO asked the National Cancer Institute’s Physician Data Query (PDQ) Adult Cancer Editorial Board to conduct an assessment of this trial to inform the PCO.
Literature Review and Analysis: IPASS

• The Iressa Pan-Asia Study (IPASS) was a phase III, multicenter, randomized, open-label, parallel-group study comparing gefitinib with carboplatin plus paclitaxel as first-line treatment for patients in East Asia who had advanced adenocarcinoma of the lung and were nonsmokers or former light smokers with other specific clinical characteristics.

• The primary outcome of interest was PFS and the trial was designed to show non-inferiority.
Literature Review and Analysis:
National Cancer Institute PDQ Editorial Review Assessment

• Upon request from ASCO, the National Cancer Institute’s PDQ Editorial Board provided a written assessment of the IPASS data (http://www.cancer.gov/cancertopics/pdq/adult-treatment-board).

• PDQ assessment of IPASS
  – met primary objective of demonstrating non-inferiority
  – showed superiority of gefitinib versus carboplatin–paclitaxel for PFS
The assessment highlighted substantive points for the PCO ad hoc panel’s consideration:

- The participants in IPASS were people from China, Japan, Korea, Thailand, and Taiwan.
- The applicability of these results to non-Asian populations with similar clinical or mutational features is uncertain.
- May be additional environmental or genotypic factors between populations that may alter sensitivity to therapy.
• Highlighted substantive points for the PCO (cont’d)
  – The magnitude of benefit from erlotinib versus chemotherapy obtained in clinical trials testing gefitinib is not currently known when using erlotinib (the only EGFR TKI now approved in the United States)
  – Extrapolations from other analyses suggest possible comparability
Integrative Discussion and Analysis

- 5 RCTs included: 4/5 PFS statistically significant improvement for mutation positive patients taking EGFR TKI
- 1\textsuperscript{st}-line EGFR TKI not beneficial for those testing negative for \textit{EGFR} mutations
- PCO applies primarily to patients with adenocarcinoma

POPULATIONS

- No significant differences in types and locations of \textit{EGFR} mutations between NSCLC of Asians and non-Asians
Integrative Discussion and Analysis

POPULATIONS

• All *EGFR* mutations in same loci of the DNA across ethnicities
  – Also true for secondary T790M and *MET* gene amplification

• Across reports of using EGFR TKIs for patients with positive mutations:
  – Similar overall response rates
  – Similar overall survival rates
Integrative Discussion and Analysis

AGENTS

• Apparent similarly results for erlotinib and gefitinib from OPTIMAL (erlotinib) and IPASS (gefitinib) trials
  • Awaiting additional results

• Extrapolating from erlotinib studies:
  • Study of 2\textsuperscript{nd}/3\textsuperscript{rd} line erlotinib: positive mutation test higher response rates
  • Study of maintenance: positive mutation test higher PFS

www.asco.org/pco/egfr ©American Society of Clinical Oncology 2011. All rights reserved - <released 04/11/11>
ASCOr’s Provisional Clinical Opinion

- Based on the results of five phase III RCTs, patients with advanced non-small cell lung cancer of the lung who are being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for EGFR mutations to determine which is an appropriate first-line therapy: an EGFR TKI or chemotherapy.
### Guideline Methodology: Update Committee Members

<table>
<thead>
<tr>
<th>Update Committee Members</th>
<th>Affiliation/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuseppe Giaccone, MD, Co-Chair</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>Vicki Leigh Keedy, MD, Co-Chair</td>
<td>Vanderbilt University Medical Center</td>
</tr>
<tr>
<td>Mary Beth Beasley, MD, FACP</td>
<td>Mount Sinai Medical Center</td>
</tr>
<tr>
<td>David H. Johnson, MD, FACP</td>
<td>University of Texas, Southwestern Medical Center</td>
</tr>
<tr>
<td>Lisa M. McShane, PhD</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>Daniel T. Milton, MD</td>
<td>Hematology/Oncology of Indiana, PC</td>
</tr>
<tr>
<td>John R. Strawn, MD</td>
<td>Patient Representative</td>
</tr>
<tr>
<td>Heather A. Wakelee, MD</td>
<td>Stanford University</td>
</tr>
</tbody>
</table>
Additional ASCO Resources

• The PCO and a patient guide can be found at: http://www.asco.org/pco/egfr

• A patient guide, “What to Know” about this PCO, is also available at: http://www.cancer.net/whattoknow
ASCO Guidelines

This resource is a practice tool for physicians based on an ASCO® Provisional Clinical Opinion (PCO). The PCO and this presentation are not intended to substitute for the independent professional judgment of the treating physician. PCOs do not account for individual variation among patients and may not reflect the most recent evidence. This presentation does not recommend any particular product or course of medical treatment. Use of the PCO and this resource is voluntary. The full PCO and additional information are available at http://www.asco.org/pco/egfr. Copyright © 2011 by American Society of Clinical Oncology®. All rights reserved.