Molecular testing in NSCLC.

P. Pauwels (UZA/UZG)

| Trial | Type | Drug | Condition or Action | BEP (% 5-FUPEI versus other) | Metastasis or treatment benefits (Overall Survival)
|-------|------|------|---------------------|------------------------------|--------------------------------------------------------
|                    |      |      |                     |                              |                                                        |
| E4301 Phase II      | Gen 1 | gefitinib | gefitinib-treated NSCLC | 54.1 versus 54.0 (5-FUPEI vs. 5-FUPEI) | 58 versus 58 (OS) |
| E4301 Phase II      | Gen 1 | gefitinib | gefitinib versus placebo | 54.1 versus 54.0 (5-FUPEI vs. 5-FUPEI) | 58 versus 58 (OS) |
| E4301 Phase II      | Gen 1 | gefitinib | gefitinib versus placebo | 54.1 versus 54.0 (5-FUPEI vs. 5-FUPEI) | 58 versus 58 (OS) |
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**Graphical Representation:**

- Combination chemotherapy (50% NSCLC) and platinum doublets (50% NSCLC) are compared in the top graph, showing overall survival (OS) for different time periods.
- The bottom graph illustrates the survival rates for patients with EGFR-mutant NSCLC compared to those with wild-type tumors.

**Table:**

- **Rows:** Trials
- **Columns:** Phase, Type, Drug, Condition or Action, BEP (% 5-FUPEI versus other), Metastasis or treatment benefits (Overall Survival)
- **Data:** Various comparisons are made, highlighting the effectiveness of different treatments in various conditions.

**Graphs:**

- The top graph shows survival rates with various chemotherapy regimens.
- The bottom graph compares survival rates between patients with EGFR-mutant and wild-type NSCLC.
EGFR

- Exist as monomers
- Binds ligand, changes shape and homo/hetero-dimerize
- Autophosphorylation of tyrosine residues
- Recruitment of adaptor/signaling molecules
- Downstream signaling
INTERESTing Biomarker to Select IDEAL Patients for Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: Yes, for EGFR Mutation Analysis, Others, I PASS

Irene S. Steadman, Division of Oncology, Department of Medicine, and the Alan J. Sklarson Cancer Center at Washington University School of Medicine, St Louis, MO

Original Article
Amplification of EGFR T790M causes resistance to an irreversible EGFR inhibitor

D Ernst, K Zepednik, K Yonesaka, Y Xiao, M Ceperchi, A Rogers, E Leikin, A Brown, C Liu, JG Christiansen, DI Kowalski, JA Engelman, and PA Janne.

Science Center for Drug Discovery, Dana Farber Cancer Institute, Boston, MA 02115. Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA 02115. Department of Radiation Oncology, Harvard Medical School, Boston, MA 02115. Department of Medicine, Brigham and Women’s Hospital, Boston, MA 02115. Adlai E. Stevenson II Center for Cancer Research at the University of Chicago, Chicago, IL 60637. Department of Medicine, Dana Farber Cancer Institute, Boston, MA 02115. Department of Radiation Oncology, Harvard Medical School, Boston, MA 02115. Department of Medicine, Brigham and Women’s Hospital, Boston, MA 02115. Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115.

Fig 1. Agents currently under development as inhibitor pathway inhibitors can be broadly subdivided into mokologics and non-structural small molecule compounds.

Cancer Cell
Preexistence and Clonal Selection of MET Amplification in EGFR Mutant NSCLC


Cell Cycle and Cancer Therapeutics Group, Department of Oncology, Dana Farber Cancer Institute, Boston, MA 02115. Department of Medicine, Dana Farber Cancer Institute, Boston, MA 02115. Department of Oncology, Dana Farber Cancer Institute, Boston, MA 02115. Department of Medicine, Dana Farber Cancer Institute, Boston, MA 02115. Department of Medicine, Dana Farber Cancer Institute, Boston, MA 02115. Department of Medicine, Dana Farber Cancer Institute, Boston, MA 02115.

Consensus for EGFR Mutation Testing in Non-small Cell Lung Cancer

Results from a European Workshop

Robert Parker, MD, PhD; Eric J. F. Sirlin, MD, PhD; Fock-Fu Koe, MD, PhD; Michael P. Hossain, MD, PhD; Marcelo Titus, PhD; David Gacera, MD; Fred B. Hohl, MD; Domingo Guevara-Aguirre, MD; Guillermo Popper, MD; Liesl Lawlira, MD; Atiye Hanehan, MD, PhD; Christian Hanania, MD; Pierre Schlumberger, MD; Michael Thomas, MD, PhD; Miguel Arriagada, MD; and Mehdi Fouladi, MD, on behalf of the European EGFR Workshop Group.
Can Cytology Samples Be Used?

Cytology samples may be suitable for analysis but further research is needed to fully understand the clinical reliability of mutational data obtained from these samples. Until then, clinicians should be encouraged to provide tissue biopsy samples whenever possible.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Recommendations for EGFR Mutation Testing In NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Which patient</strong>?</td>
<td>NSCLC patient*</td>
</tr>
<tr>
<td><strong>Time point</strong></td>
<td>At diagnosis</td>
</tr>
<tr>
<td><strong>Sample source</strong></td>
<td>Where possible at disease progression</td>
</tr>
<tr>
<td><strong>More easily accessible</strong></td>
<td>Biopsy performed over cystology</td>
</tr>
<tr>
<td><strong>10%; central/nasal/biopsy</strong></td>
<td>Bront’s fluid should not be used</td>
</tr>
<tr>
<td><strong>Toxic cell content</strong></td>
<td>Tox cells for DNA</td>
</tr>
<tr>
<td><strong>Interpreting</strong></td>
<td>Separating</td>
</tr>
<tr>
<td><strong>EGFR mutations analysis method</strong></td>
<td>Lumen % acceptable with higher sensitivity techniques</td>
</tr>
<tr>
<td><strong>Report to include</strong></td>
<td>No gold standard yet</td>
</tr>
<tr>
<td><strong>Definition of biopsy sample and tissue</strong></td>
<td>Detal of biopsy sample and tissue return</td>
</tr>
<tr>
<td><strong>Type of mutation analysis</strong></td>
<td>Mutation presentation interpretation</td>
</tr>
</tbody>
</table>

*Local policy may determine what patients are tested. In European studies, the persistence of EGFR mutation is in relator diagnosed separate cell carcinomas, adenocarcinoma, squamous cell carcinoma, and undifferentiated bronchopulmonary adenocarcinoma is approximately one. A pragmatic approach could be used for testing these patients with candidate biopsies of the above tumor types. This is not a list of those with known responses to therapy. Consideration of response type is necessary in which categories are not tested to be defined.

NSCLC: non-small cell lung cancer.

**Clinical Activity Observed in a Phase 1 Dose-Escalation Trial of an Oral MET and ALK Inhibitor, PF-02341066**

EL Kwak,1 DR Carney,2 J Clark,1 GI Shapilo,3 RG Mak,4 MJ Ratain,5 B Solomon,6 Y-J Bang,7 S-H Cu,8 R Salgia9

1. Massachusetts General Hospital 5. University of Chicago Cancer Center
2. University of Colorado Cancer Center 6. Peter MacCallum Cancer Centre
3. Dana-Farber Cancer Institute 7. Seoul National University
4. Memorial Sloan-Kettering Cancer Center 8. University of California at Irvine
Summary

- Treatment with crizotinib resulted in impressive clinical activity in patients with ALK-positive advanced NSCLC
  - ORR: 57%
  - DCR at 8 weeks: 87%
  - PFS probability at 6 months: 72%
- Crizotinib was well tolerated
  - The most frequent adverse events were mild and moderate gastrointestinal events and mild visual disturbances

**EML4-ALK: Honing In on a New Target in Non–Small-Cell Lung Cancer**

**The NEW ENGLAND JOURNAL of MEDICINE**

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

**FISH Assay for ALK Rearrangement**

- Tricorner 2p23 region
- Centromere (2;2) ALK gene break point region
- Break-apart FISH assay for ALK fusion genes**