Date of request: July 10, 2015
NCCN Guidelines Panel: Non-small Cell Lung Cancer

To the NCCN panel members:

On behalf of Foundation Medicine Inc., I respectfully request the NCCN Non-Small Cell Lung Cancer Panel to review the following information and thereafter recommend validated comprehensive genomic profiling (VCGP) assays to support targeted therapy selection and clinical trial enrollment for patients with non-small cell lung cancer (NSCLC).

We define VCGP as hybrid capture based, next-generation sequencing testing with high unique coverage (>250x) of hundreds of cancer-related genes capable of detecting all four classes of genomic alterations (base pair substitutions, insertion/deletions, copy number alterations, rearrangements) from a single assay with analytic validation published in a peer reviewed journal. We feel it is critical that patients, being assessed for enrollment in a clinical trial of molecularly targeted therapy, be tested with VCGP, given that patients on molecularly matched clinical trials have been suggested to have superior RR, PFS\(^1\) and OS versus those on unmatched trials.\(^1,3\)

Specific Changes:

1. On page NSCL-16 of the NCCN Guidelines Version 7.2015 (11 JUNE 2015) in the 3\(^{rd}\) bullet point of the algorithm diagram annotated by footnote “hh”, we request changing language from:

   Current Language: “\(\text{EGFR} \text{ and } \text{ALK} \) testing should be conducted as part of multiplex/next generation sequencing [NGS]”

   To Requested Language: “\(\text{EGFR} \text{ and } \text{ALK} \) testing should be conducted as part of validated comprehensive genomic profiling of cancer-related genes so as to identify the full range of targeted treatment options or ongoing clinical trials,” for all histological subtypes.

2. In addition, we request accordingly changing the text of the “hh”, footnote on page NSCL-16 from:

   Current Language: “NCCN NSCLC Guidelines Panel strongly endorses broad molecular profiling ….”

   To Requested Language: “NCCN NSCLC Guidelines Panel strongly endorses validated comprehensive genomic profiling ….”

Rationale: The NCCN’s endorsement for “broader molecular profiling” of NSCLC tumors (NSCL-16, footnote “hh”) has been an important step in advancing precision medicine in this disease. It has been demonstrated that the use of validated CGP is superior to other approaches for identifying genomic alterations associated with sensitivity to targeted therapies suggested in the NCCN Guidelines. In one study, 26% of NSCLC patients who had tested negative by extensive “hotspot”\(^*\) and FISH tests still harbored a genomic alteration associated with a therapy within NCCN guidelines.\(^4\) Beyond the well-known genomic driver alterations (NSCL-H), NSCLC can harbor other clinically relevant alterations associated with both sensitivity and resistance to targeted therapies that can assist in optimizing clinical trial selection for eligible patients. See examples in Table 1 below.
* “hotspot” is defined as an area in a gene of interest with a known high incidence of point mutations and base pair insertions/deletions tested for by PCR based assays.

<table>
<thead>
<tr>
<th>Genomic Alteration (i.e. Driver event)</th>
<th>Available targeted agents with activity against driver event in Non-small cell lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong> V600E mutations**</td>
<td>Vemurafenib(^5), Dabrafenib (^6)</td>
</tr>
<tr>
<td><strong>MET</strong> amplification</td>
<td>Crizotinib(^7,8)</td>
</tr>
<tr>
<td><strong>ROS1</strong> rearrangements</td>
<td>Crizotinib(^9)</td>
</tr>
<tr>
<td><strong>HER2</strong> mutations</td>
<td>Trastuzumab(^10), Afatinib(^11)</td>
</tr>
<tr>
<td><strong>RET</strong> rearrangements</td>
<td>Cabozantinib(^12)</td>
</tr>
</tbody>
</table>

Table 1

**Non-V600E mutations have variable kinase activity and response to these agents

Further evidence is continuing to emerge that other types of alterations in these genes can cause oncogenic events that can either be targets for molecular therapies or confer resistance to such treatments. For example, Frampton et al., and others have reported recently that splice site mutations in MET exon 14 that will render tumors responsive to ALK or MET inhibitors.\(^{13,14}\) Conversely mutations in ALK have now been documented to cause resistance to certain targeted therapies\(^{15,16,17}\).

Validated CGP has identified an expanded set of targetable genomic alterations that can be treated with drugs approved specifically for NSCLC or currently under clinical investigation. The goal should not be to “sample” targetable driver alterations through narrow molecular testing, but to simultaneously evaluate all cancer-related genes to find alterations that might render sensitivity to a targeted therapy and thus have an impact on clinical trial eligibility and stratification (Figure 1). Results from validated CGP may be superior to other approaches, and have the potential to identify known and novel oncogenic alterations in this disease that may guide precision therapy trial selection (see Figure 2).\(^4\)

Additionally, there are greater than 200 active trials for targeted agents that target genomic alterations of oncogenic drivers or altered signal transduction pathways (see Table 2 attached). Therefore, due to both the greater breadth, and superior sensitivity and specificity of validated CGP, more patients can be identified for targeted therapy.\(^18\)

Validation of CGP assays should demonstrate high sensitivity and specificity (95-99% sensitivity, PPV >99%) across all classes of alterations determined through testing of clinical samples (> 20% tumor content) and cell line models. Additionally, sequencing should cover the entire coding regions of cancer-related genes to a median unique sequencing depth of >250x to ensure that all classes of clinically relevant alterations will be detected, thus maximizing the number of therapeutic targets and increasing treatment options for patients including clinical trials. Conservation of tissue using this approach helps ensure that genomic alterations are not missed due to limitations in tissue availability or purity, and reduces the risk of repeat biopsy procedures.\(^19,20,21\)

We appreciate the panel’s consideration of this request and are hopeful that it will arrive at a recommendation that continues to improve options and outcomes for NSCLC patients, as well as encourage enrollment in clinical trials. Should you have any questions about the information in our submission, please do not hesitate to contact me.

Sincerely,

Vincent Miller, MD
Chief Medical Officer
Foundation Medicine, Inc.
REFERENCES


3. Wheler, Jennifer J. RY, Bettzy Stephen, David S. Hong, Ralph Zinner, Vivek Subbiah, Siqing Fu, Daniel D. Karp, Gerald Steven Falchok, Aung Naing, Apostolia Maria Tsimberidou, Sarina Anne Piha-Paul, Filip Janku, Yali Li, J. Jack Lee, Vincent A. Miller, Funda Meric-Bernstam, Razelle Kurzrock; Department of Investigational Cancer Therapeutics (Phase 1 Program), The University of Texas MD Anderson Cancer Center, Houston, TX; Foundation Medicine, Inc., Cambridge, MA; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX; Sarah Cannon Research Institute at HealthONE, Denver, CO; Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; UC San Diego, San Diego, CA. Prospective study comparing outcomes in patients with advanced malignancies on molecular alteration-matched versus non-matched therapy. 2015(J Clin Oncol 33, 2015 (suppl; abstr 11019)).


18. FMI Data On File MAY 2015


21. CMS Palmetto Local Coverage Determination: MolDx: NSCLC,Comprehensive Genomic Profiling Testing
