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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 3rd bullet point of the algorithm diagram annotated by footnote "hh", we request changing language from:

Current Language: "*EGFR* and *ALK* testing should be conducted as part of multiplex/next generation sequencing [NGS]"
To Requested Language: "*EGFR* and *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.

Genomic Alteration (i.e. Driver event)	**Available targeted agents with activity against driver event in Non-small cell lung cancer**
BRAF V600E mutations**	Vemurafenib[5], Dabrafenib [6]
MET amplification	Crizotinib [7,8]
ROS1 rearrangements	Crizotinib[9]
HER2 mutations	Trastuzumab[10,] Afatinib[11]
RET rearrangements	Cabozantinib[12]

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 ($\geq$ 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,

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REFERENCES

1. Tsimberidou AM, Iskander NG, Hong DS, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res.* Nov 15 2012;18(22):6373-6383.
2. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *Jama.* May 21 2014;311(19):1998-2006.
3. Wheler, Jennifer J. RY, Bettzy Stephen, David S. Hong, Ralph Zinner, Vivek Subbiah, Siqing Fu, Daniel D. Karp, Gerald Steven Falchook, 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)).
4. Drilon A, Wang L, Arcila ME, et al. Broad, Hybrid Capture-Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches. *Clin Cancer Res.* Jan 7 2015.
5. Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* Oct 2012;7(10):e23-24.
6. Planchard D, Mazieres J, Riely GJ, *et al.* Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients. *J Clin Oncol* 2013; 31(Suppl 15): 8009. Abstract
7. Ou SH, Kwak EL, Siwak-Tapp C, *et al.* Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. *J Thorac Oncol* 2011 May; 6(5):942-6. PMID: 21623265. Available at: http://journals.lww.com/jto/Fulltext/2011/05000/Activity_of_Crizotinib__PF02341066_,_a_Dual.15.aspx
8. Camidge, RD, Ou S-Hi, Shapiro G, *et al.* Efficacy and safety of crizotinib in patients with advanced c-MET amplified non-small cell lung cancer. *J Clin Oncol* 2014; 32(Suppl 5): 8001. Abstract
9. Shaw, A. T., & Solomon, B. J. (2015). Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med, 372*(7), 683-684. doi: 10.1056/NEJMc1415359
10. Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. *The New England journal of medicine.* Jun 15 2006;354(24):2619-2621.
11. Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jun 1 2013;31(16):1997-2003.
12. Drilon A, Wang L, Hasanovic A, et al. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov.* Jun 2013;3(6):630-635.
13. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov.* May 13 2015.Frampton et al., 2015;PMID 25971938
14. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer discovery.* May 13 2015.
15. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *The New England journal of medicine.* Oct 28 2010;363(18):1734-1739.

16. Friboulet L, Li N, Katayama R, et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. *Cancer discovery.* Jun 2014;4(6):662-673.
17. Ou SH, Klempner SJ, et al. Identification of a novel HIP1-ALK fusion variant in Non-Small-Cell Lung Cancer (NSCLC) and discovery of ALK I1171 (I1171N/S) mutations in two ALK-rearranged NSCLC patients with resistance to Alectinib Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 9:12 2014 Dec pg 1821-5Ou SH, Klempner SJ, 2014 PMID 2539376
18. FMI Data On File MAY 2015
19. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol.* Nov 2013;31(11):1023-1031.
20. Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. *The Journal of molecular diagnostics : JMD.* May 2015;17(3):251-264.
21. CMS Palmetto Local Coverage Detemination: MolDx: NSCLC,Comprehensive Genomic Profiling Testing

LCD ID L36143. Published 7/6/2015 http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx -accessed 7/6/2015

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