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**NCCN Guidelines Panel:** Non-small Cell Lung Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Non-small Cell Lung Cancer Guideline Panel review the enclosed data supporting updates to the Guidelines and inclusion of FoundationOne®, our currently available assay, and FoundationOne CDx™, currently under parallel and expedited review by FDA and CMS with anticipated approval in the second half of 2017, as examples of “broad molecular profiles” in the work-up of patients with metastatic non-small cell lung cancer. With FoundationOne CDx, the specific tumor types are those in which current companion diagnostics exist, including this NSCLC submission, and melanoma, breast, colorectal and ovarian cancers to be submitted separately but contemporaneously for NCCN consideration. It is anticipated that this comprehensive genomic assay will be FDA approved for all solid tumors and that a CMS NCD (National Coverage Determination) will be issued at the time of approval. The assay covers 324 genes and respective companion diagnostics in these diseases. In order to achieve this broad approval, the ongoing process, unlike conventional bridging studies associated with disease specific clinical validation studies, involved a submission with genomic analysis of more than 6,000 samples across all four classes of genomic alterations (base substitutions, indels, copy number variations and rearrangements). In addition to calling variants across these genes and indicating the relevant companion diagnostics, genomic signatures for MSI (microsatellite instability) and TMB (tumor mutational burden) are anticipated in the intended use. Validation and concordance was demonstrated in more than 36 distinct tumor types and across a spectrum of specimen types-including fine needle aspirations. The FoundationOne CDx assay will thus serve as a single test to identify patients whose tumors contain alterations tied to currently FDA approved therapies and also as a molecular screen to facilitate and expedite access to clinical trials, overall permitting more rapid testing of novel therapies and shortening the time and cost of drug development.

**Specific Changes:** In addition to the specific addition of FoundationOne and FoundationOne CDx as example “*broad molecular profiles*”, we request to move the alterations currently listed in the “Emerging Targeted Agents for Patients with Genetic Alterations” table on page NSCL-H of the Guidelines into the algorithm for metastatic NSCLC patients on page NSCL-17. These alterations include *BRAF* V600E, high-level *MET* amplification, *MET* exon 14 skipping mutations, *RET* rearrangements, and *HER2* mutations. Additionally, we urge that the “broad molecular profiling” described in the treatment algorithm on page NSCL-17, should be clarified to specify that the profiling is optimally completed as part of a single assay, in order to conserve tissue and to obtain as much information as possible at the time of diagnosis. Finally, we also request that the following genomic alterations be listed in the “Emerging Targeted Agents for Patients with Genetic Alterations” table on page NSCL-H: high TMB, *EGFR* fusions, and *NTRK* fusions.

**FDA Clearance:** FoundationOne is a laboratory developed test (LDT) currently available for clinical use, and FoundationOne CDx is currently under parallel and expedited review by FDA and CMS with anticipated FDA approval the second half of 2017.

**Rationale:** *BRAF* V600E is an established target in melanoma, and is sensitive to approved *BRAF* V600-specific inhibitors alone or in combination with *MEK* inhibitors. Recent results from a phase 2 trial of dabrafenib + trametinib showed an overall response rate in previously treated *BRAF* V600-positive NSCLC patients of 63.2% (36/57) and a median PFS of 9.7 months [1]. Dabrafenib + trametinib was recently approved by the European Medicines Agency for treatment of patients with *BRAF* V600-positive advanced NSCLC.

*MET* exon 14 skipping mutations have been established as driver alterations therapeutically targetable by crizotinib, which is approved in NSCLC for *ALK* and *ROS1* fusions. Several series have shown that these alterations are found in approximately 3% of lung carcinomas and respond to crizotinib [2, 3]. Multiple phase 2 trials of *MET* inhibitors in

NSCLC patients with *MET* exon 14 mutations are ongoing. *MET* amplification is also an established target in cancer, and responses to crizotinib have been reported in NSCLC [4, 5].

*RET* rearrangements are present in 1-2% of NSCLC and are targetable by several multi-kinase inhibitors approved in other tumor types. Phase 2 trials of *RET* inhibitors in NSCLC patients with *RET* rearrangements are ongoing, and data from a multicenter registry of 165 patients with *RET*-rearranged NSCLC showed response rates of 37%, 18%, and 22% for cabozantinib, vandetanib, and sunitinib, respectively [6].

Diverse *HER2* mutations have been identified as oncogenic drivers in NSCLC and are targetable by afatinib, as well as other *HER2* inhibitors in development or approved in other tumor types. In studies of NSCLC patients with *HER2* exon 20 insertion mutations treated with *HER2*-targeted therapies, response rates of over 50% have been observed [7]. Recently, *HER2* transmembrane domain mutations have also been identified in driver-negative NSCLCs, and patients with these mutations responded to afatinib [8].

More comprehensive testing at the time of metastatic diagnosis is also expected to identify rare genomic drivers that are indeed therapeutically targetable, and potential modifiers of response to therapies which target oncogenic drivers (e.g., co-occurrence of a *BRAF* mutation in an *EGFR*-mutated tumor). Importantly, broad molecular profiling is expected to inform the patient's treatment plan, including the option to enroll in a genomically matched clinical trial. In one study, of 47 patients negative for driver alterations via non-NGS testing, non-NGS testing resulted in tissue exhaustion and repeat biopsy was not possible or was declined by the patient in 34% of cases. In the remaining patients with available tissue, a potentially targetable genomic alteration was subsequently identified by hybrid-capture based NGS testing in 20/31 cases [9].

High TMB in NSCLC has been reported as a predictive biomarker for response to approved immune checkpoint inhibitors [10–12]. *EGFR* fusions in NSCLCs negative for *EGFR* mutations and other driver alterations were recently identified, and 4/4 patients treated with approved *EGFR* inhibitors had partial responses [13]. *NTRK* rearrangements have been identified as driver alterations in ~3% of NSCLC, and potent *NTRK* inhibitors are now in clinical development in NSCLC and other solid tumors. In the phase 2 trials of entrectinib and LOXO-101, confirmed responses were observed in 8/10 solid tumor patients with *NTRK* fusions overall, including 2 NSCLC patients, one of whom remains on study after 17 months [14, 15].

Consistent with the NCCN recommendation to steer patients to therapeutic clinical trials, hybrid capture comprehensive genomic profiling (CGP), like FoundationOne and FoundationOne *CDx*, finds alterations (*EGFR* mutations, *ALK*, *RET*, *ROS1*, *NTRK*, *EGFR*, *FGFR*, *BRAF* and *RAF1* fusions, *BRAF* mutations, *MET*, *HER2*, *FGFR*, or *KIT* amplification/mutation, *BRCA1/2*, *TSC1/2*, *NF1/2*, or *PTEN* inactivating alterations, *CDK4/6* or *CCND1/2/3* amplification, *IDH1/2*, *PIK3CA*, *AKT*, *mTOR*, or *MEK1* mutations, high MSI, high TMB, etc.) that indeed provide a match to targeted therapies in clinical trials in >80% of patients with NSCLC. Foundation Medicine has recently joined NCI-MATCH and anticipates imminently joining TAPUR in a formal role using the combination of CGP and clinical trial matching to accelerate accrual to these transformative efforts. Taken together, these data suggest CGP is an essential addition to clinical care of patients with this often deadly malignancy.

Thank you for your review of this submission.

Sincerely,



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