Submitted by: Vincent A. Miller, MD
Company: Foundation Medicine, Inc.
Address: 150 Second Street, Cambridge, MA 02141
Phone: 617-418-2259
Email: vmiller@foundationmedicine.com
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NCCN Guidelines Panel: Non-small cell lung cancer (NSCLC)

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Non-small Cell Lung Cancer (NSCLC) Guideline Panel to consider the requested updates and enclosed references, pertaining to the evaluation and management of patients with NSCLC.

Specific Changes and Rationale:

1. **Include Tumor Mutational Burden (TMB) in the list of biomarkers that should be tested as part of the work-up of a patient with metastatic NSCLC on page NSCL-H of the Guidelines.** TMB in NSCLC has been reported as a predictive biomarker for response to immune checkpoint inhibitors including anti-PD-1 or anti-PD-L1-based monotherapy, as well as for combination anti-PD-1 and anti-CTLA4 therapy [1-7]; high TMB has been associated with improved outcomes to immune checkpoint inhibitors independent of PD-L1 expression [1, 2, 4, 5].

   In retrospective analyses of several clinical trials of the anti-PD-1 inhibitor nivolumab, anti-PD-L1 inhibitor atezolizumab, or the combination of nivolumab plus the anti-CTLA4 inhibitor ipilimumab, TMB was predictive of improved overall survival, progression-free survival (PFS), response rate and/or durable clinical benefit [1, 3, 4].

   In the Phase 3 Checkmate-227 trial of first-line nivolumab plus ipilimumab for patients with stage IV or recurrent NSCLC [3], TMB was predictive of improved PFS (7.2 months for nivolulmab/ipilimumab versus 5.5 months for chemotherapy), 1-year PFS rate (42.6% for nivolumab/ipilimumab versus 13.2% for chemotherapy), and response rate (45.3% nivolulmab/ipilimumab versus 26.9% for chemotherapy); TMB in this trial was determined using the FoundationOne CDx assay [2].

2. **Include guidance regarding the measurement of TMB in the "Principles of Molecular and Biomarker Analysis" section that begins on page NSCL-G.** Publications indicate that the accuracy of TMB decreases when less than 0.5-0.8Mb of DNA are evaluated and it is imperative that the assays being used by physicians are analytically and clinically validated [8,9].

3. **Clarify that the "broad molecular profiling" described in the treatment algorithm on page NSCL-17, 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 to inform the use of currently available biomarker driven therapies as well as clinical trial options.**

FDA Clearance: TMB is currently reported as part of FoundationOne CDx™, an FDA-approved broad companion diagnostic that is clinically and analytically validated for solid tumors.

Thank you for your review of this submission.

Sincerely,

Vincent A. Miller, M.D.
Chief Medical Officer
Foundation Medicine

References

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6. Forde PM, Chaft JE, Smith KN et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *N. Engl. J. Med.* 2018: NEJMoa1716078.

7. Rizvi NA, Hellmann MD, Snyder A et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* 2015; 348(6230):124–128.

8. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med.* 2017;9(1):34.

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