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NCCN Guidelines Panel:	Non-Small Cell Lung Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Non-Small Cell Lung Cancer (NSCLC) to review the enclosed data on liquid biopsy, or ctDNA testing, for the appropriate identification of driver gene mutation positive patients eligible for targeted therapy and provide appropriate guidance on the clinical utility of liquid biopsy, or ctDNA testing.

Specific change: We respectfully request the enclosed data to be considered for inclusion as appropriate within the guidelines.

1. Updating the NSCL-G (page 5 of 5) to reflect the latest advances in ctDNA testing for the identification of driver gene mutation positive patients, and to provide guidance on utilizing ctDNA testing as a complimentary testing option for identifying driver gene mutations in patients with metastatic NSCLC.

Rationale for updating plasma testing on NSCL-G (page 5 of 5): Based on the latest scientific evidence for plasma testing, the Food and Drug Administration has approved plasma-based companion diagnostic (CDx) tests for the detection of sensitizing driver-gene mutations for multiple targeted therapies.[1] The latest scientific data has demonstrated non-inferiority of ctDNA testing to tissue testing for the identification of metastatic NSCLC patients for targeted therapy.[2] Recent data also suggest that, while tissue testing or ctDNA testing each has its limitations, concurrent plasma- and tissue-based testing could identify most patients with therapeutically targetable mutations, therefore reducing the proportion of patients with "unknown" genotype status.[3] Up to 1 in 3 patients may have insufficient tissue for molecular testing or tissue biopsy may not be feasible, limiting detection of actionable mutations.[3] Plasma-based testing could be used at diagnosis to identify biomarker mutations in these patients.[4] Also, plasma-based testing may improve biomarker discovery rate and turnaround time compared with standard-of-care tissue-based testing. In a prospective study evaluating next-generation sequencing as a testing platform, cell-free DNA results were returned significantly faster than tissue results (9 vs. 15 days, $p<0.0001$). Additionally, in this study, plasma-based testing had 80% clinical sensitivity for any guideline recommended biomarker and detected an additional 29 patients positive for actionable biomarkers not detected by tissue-based testing, including those with negative, not assessed, or insufficient tissue results.[2]

Plasma-based testing may be complimentary to tissue-based testing in the metastatic NSCLC patient population and could identify patients for targeted therapy that would otherwise be missed due to tissue testing complications or timing constraints.[2,3]

Sincerely,

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[1] FDA companion diagnostics website. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed August 2, 2019.

[2] Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. *Clin Cancer Res*. 2019;25(15):4691-4700.

[3] Aggarwal C, Thompson JC, Black TA, et al. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. *JAMA Oncol*. 2019;5(2):173-180.

[4] Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. *Arch Pathol Lab Med*. 2018;142:321-346.