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October 6, 2014

Submitted by:
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Date of request: October 6, 2014
NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Dear Sir or Madam,

On behalf of Oncology Analytics, Inc., we respectfully request that the NCCN Non-Small Cell Lung Cancer panel review our proposal to remove specific category 2A guideline/compendium listings that have a low level of evidence.

Specific Changes:

1. Please consider removing the following drugs from the NCCN Drugs & Biologics Compendium for NSCLC.¹
 - Vemurafenib: Category 2A for Non-Small Cell Lung Cancer (NSCLC); NCCN recommended use: Activity against BRAF mutations in lung cancer
 - Dabrafenib: Category 2A for Non-Small Cell Lung Cancer (NSCLC); NCCN recommended use: Activity against BRAF mutations in lung cancer
 - Cabozantinib: Category 2A for Non-Small Cell Lung Cancer (NSCLC); NCCN recommended use: Activity against RET gene rearrangements in lung cancer
2. Please consider removing the following agents from the table titled, "Targeted Agents for Patients with Genetic Alterations" located on Page 59 (NSCL-H) of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Non-Small Cell Lung Cancer (version 4.2014):²
 - BRAF mutation: vemurafenib, dabrafenib
 - RET rearrangements: cabozantinib

FDA Clearance:

Neither vemurafenib, dabrafenib, nor cabozantinib are FDA-indicated for NSCLC.

Rationale:

There is inadequate scientific data to support a category 2A designation for vemurafenib, dabrafenib and cabozantinib in the NCCN Guidelines and the Drugs & Biologics Compendium for NSCLC. A category 2A recommendation mandates that these medications be covered by public and private insurers alike, including the Centers for Medicare & Medicaid Services (CMS). However, the safety and efficacy of using these agents in a significant number of NSCLC patients is currently unknown.

In an attempt to understand the NCCN uniform consensus that led to the category 2A recommendation for these agents in NSCLC, Oncology Analytics reviewed the NCCN Transparency Process and Recommendations. Unfortunately, Oncology Analytics was unable to find the transparency document(s) relating to the addition of vemurafenib, dabrafenib, and cabozantinib as a NSCLC category 2A recommendation.

The NSCLC NCCN Guideline table titled, "Targeted Agents for Patients with Genetic Alterations," lists references to support the category 2A recommended use for vemurafenib, dabrafenib, and cabozantinib. These references include a case report for vemurafenib, an ASCO abstract to support dabrafenib, and preliminary data on three patients that received cabozantinib in an ongoing clinical trial.³⁻⁵ This constitutes a low level of evidence.

Given these sources, the NCCN listed references for vemurafenib, dabrafenib, and cabozantinib would not be supported as off-label, medically necessary treatment by the Centers for Medicare & Medicaid Services (CMS) according to the Medicare Benefit Policy Manual transmittals, Chapter 15:50.4.5, titled Off Label Use of Anti-Cancer Drugs and Biologics which states the following:⁶

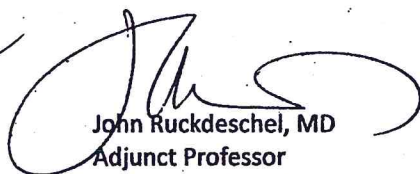
- **C. Use Supported by Clinical Research That Appears in Peer-Reviewed Medical Literature**
 - Contractors may also identify off-label uses that are supported by clinical research under the conditions identified in this section...Abstracts (including meeting abstracts) are excluded from consideration.
 - In determining whether an off-label use is supported, the contractors will evaluate the evidence in published, peer-reviewed medical literature listed below. When evaluating this literature, they will consider (among other things) the following:
 - Whether the study is appropriate to address the clinical question. The contractor will consider:
 - That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs
 - That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

Although clinical trials may be underway, it is premature to list these agents as category 2A. This has the potential to adversely impact patient care. The safety and efficacy of using these agents in a significant number of NSCLC patients is currently unknown. Accordingly, we respectfully request revision of the NSCLC NCCN Guideline and the NCCN Drugs & Biologics Compendium. Thank you for your consideration.

Respectfully submitted,



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Oncology Analytics, Inc.



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References:

1. Non-Small Cell Lung Cancer (NSCLC) Version 4.2014. NCCN Drugs & Biologics Compendium. Available from: http://www.nccn.org/professionals/drug_compendium/MatrixGenerator/Matrix.aspx?DiseaseID=10. Accessed: October 2, 2014.
2. Non-Small Cell Lung Cancer (NSCLC) Version 4.2014. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nslc. Updated: June 5, 2014. Accessed: October 2, 2014.
3. Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol 2012;7:e23-24.
4. Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BR113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients [abstract]. J Clin Oncol 2013;31(Suppl 15): Abstract 8009.
5. Dilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013;3:630-5.
6. Medicare Benefit Policy Manual. Chapter 15 – Covered Medical and Other Health Services. Transmittals for Chapter 15: 50.4.5 – Off Label Use of Anti-Cancer Drugs and Biologics. Available at: <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS012673.html>. Rev. 193; Updated: August 29, 2014. Accessed: October 2, 2014.