NCCN Guidelines Panel: Non-Small Cell Lung Cancer
National Comprehensive Cancer Network
500 Old York Road, Suite 250
Jenkintown, PA 19046
Re: Petition to amend NCCN guidelines on the use of bevacizumab in initial management of advanced NSCLC

Dear Sir/Madam;

On behalf of Oncology Analytics, we respectfully request that the NCCN Non-Small Cell Lung Cancer Guideline Panel review the currently available data for the use of bevacizumab in the treatment of patients with NSCLC.

Specific changes: We request the following for consideration:

1. Specification that bevacizumab be used only in combination with carboplatin-paclitaxel, as category 1, in the initial management of advanced non-squamous NSCLC.
2. Bevacizumab-pemetrexed maintenance (currently category 2A) be removed as a continuation maintenance regimen, and bevacizumab be only used as single agent continuation maintenance.
3. Footnotes be added stating that subset analyses and retrospective studies failed to demonstrate an improvement in overall survival when bevacizumab is added to chemotherapy in elderly patients with NSCLC.

FDA status: Bevacizumab is approved by the FDA in the United States for the treatment of non-squamous NSCLC only in combination with carboplatin-paclitaxel.

ASCO and Canadian Guidelines: These two guidelines are consistent with the FDA position, and specify usage of bevacizumab with carboplatin-paclitaxel.

ESMO Guidelines: ESMO recommends usage only with carboplatin-paclitaxel and with cisplatin-gemcitabine, though they state that the OS data was negative with the cisplatin-gemcitabine combination.

Rationale for recommended changes:
The recently published results of the PointBreak trial failed to show OS or RR benefit of carboplatin-pemetrexed + bevacizumab when compared to
carboplatin-paclitaxel + bevacizumab. The trend of OS was in favor of the
carboplatin–paclitaxel + bevacizumab arm. The trial also did not show any
advantage of one arm over the other with respect to toxicities. The improvement
in the secondary endpoint of PFS was clinically insignificant.

Among the other two phase III studies (E4599 and AVAil), only E4599 showed an
OS benefit while AVAil was negative on the OS outcome.

Suggesting that pemetrexed, a much more costly agent than paclitaxel, may be
used in combination with bevacizumab in the absence of level 1 or 2A data, adds
significant cost to the care of each such lung cancer patient so treated with no
reasonable expectation of additional benefit. This recommendation also burdens
society, without any proven expected benefit.

It is also well established in patients with breast cancer that the benefit of
bevacizumab depends on the associated chemotherapy. This led the NCCN to
change its guidelines, now specifying that bevacizumab be added only to
paclitaxel.

Data to support the requested amendment:

This request to amend the NCCN NSCLC guidelines is based on pivotal positive
and negative studies that are briefly described in the accompanying synopsis.

The following articles / presentations are also submitted in support of the
proposed changes.

1. Sandler A et al. Paclitaxel-carboplatin alone or with bevacizumab for non-

2. Ramalingam SS et al. Outcomes for elderly, advanced stage NSCLC patients
treated with bevacizumab in combination with carboplatin and paclitaxel:

3. Zhu J et al. Carboplatin and Paclitaxel With vs Without Bevacizumab in
Older Patients With Advanced Non–Small Cell Lung Cancer. JAMA

4. Reck M et al. Overall survival with cisplatin–gemcitabine and bevacizumab
or placebo as first-line therapy for non-squamous non-small-cell lung
cancer: results from a randomised phase III trial (AVAil). Ann Oncol. 2010;
21(9):1804-9

5. Patel J et al. Randomized, open-Label, phase III, superiority study of
pemetrexed + carboplatin + bevacizumab followed by maintenance pem +
bev versus paclitaxel +carboplatin +bev followed by maintenance bev in
patients with stage IIIIB or IV Non-Squamous NSCLC. Multidisciplinary
symposium in Thoracic Oncology. Sep 2012

6. Azzoli CG et al. 2011 Focused Update of 2009 ASCO Clinical Practice
Guideline Update on chemotherapy for Stage IV NSCLC. J Clin Oncol. 2011;


We appreciate the opportunity to provide this information for consideration by the NCCN NSCLC panel. If you have any questions, please do not hesitate to contact me at 1-888-916-2616 or via email at marc@oncologyanalytics.com

Thank you for your time and consideration.

Sincerely,

Marc Fishman, MD

William Hrushesky, MD, FACP
William Shimp, MD
James Krook, MD
Laura Bobolts, PharmD, BCOP

Enclosures:
Synopsis
Table of proposed changes
References enumerated above