

July 18, 2016

NCCN Guidelines Panel: Head and Neck Cancer
National Comprehensive Cancer Network
275 Commerce Dr., Suite 300
Fort Washington, PA 19034

Re: Request for Addition of technetium Tc 99m tilmanocept to the NCCN Guidelines as Radiolabeled Diagnostic Agent for Clinically Node-Negative Squamous Cell Carcinoma of the Oral Cavity

NCCN Guidelines Panel: Head and Neck Cancers

On behalf of Navidea Biopharmaceuticals and its cancer patient recipients of *technetium Tc99m tilmanocept*, I respectfully request the NCCN Head and Neck Cancers Panel to review the enclosed data for the inclusion of *technetium Tc 99m tilmanocept* as a diagnostic agent for use in sentinel lymph node biopsy in early stage oral cancer, where sentinel lymph node biopsy is recognized and cited as a treatment alternative in version V1.2016 NCCN update.

Specific Changes: In section OR-2, we respectfully request *technetium Tc 99m tilmanocept injection* be added as a radiolabeled, diagnostic agent in sentinel lymph node biopsy for clinically node-negative squamous cell carcinoma of the oral cavity.

In addition, we suggest the inclusion of the new data and associated references within the narrative section of the Guidelines, specifically on page Surg-A 6 of 8 of version V1.2016, where the current data on Sentinel Lymph Node Biopsy are included.

FDA Clearance: The FDA approved *technetium Tc 99m tilmanocept* as a “radioactive diagnostic agent indicated with or without scintigraphic imaging for: (1) Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in patients with solid tumors for which this procedure is a component of intraoperative management. (2) Guiding sentinel lymph node biopsy using a handheld gamma counter in patients with clinically node-negative squamous cell carcinoma of the oral cavity, breast cancer and melanoma”.¹

Mechanism of Action: *Technetium Tc 99m tilmanocept* is the only approved, radioactive diagnostic agent for clinically node negative squamous cell carcinoma of the oral cavity. It accumulates in lymphatic tissue as the only receptor targeted agent that selectively binds to mannose binding receptors (CD206) located on the surface of macrophages and dendritic cells within the sentinel lymph node(s).

Rationale: In support of the requested changes, on June 13th 2014, the FDA granted *technetium Tc 99m tilmanocept* approval for “guiding sentinel lymph node biopsy with or without scintigraphic imaging in clinically node negative squamous cell carcinoma of the oral cavity”¹ based on a prospective Phase III, multicenter, non-randomized, single-arm trial (ClinicalTrials.gov identifier NCT00911326; <https://clinicaltrials.gov/ct2/show/NCT00911326?term=tilmanocept&rank=9>) involving 85 patients who received *technetium Tc 99m tilmanocept*.²

Data from this phase 3 study demonstrated a false negative rate (FNR) of 2.6%, accuracy of 98.8%, negative predictive value (NPV) of 97.8% and no serious adverse events related to *technetium Tc 99m tilmanocept*. These data were published in the Annals of Surgical Oncology (*Ann Surg Oncol.* **2015**;22:3708-3715) and in the Journal of the American

Medical Association-Otolaryngology (*JAMA-Otolaryng.* **2013**; 139:895-902). *Technetium Tc 99m tilmanocept* also showed a significantly improved FNR and NPV when compared to results of the ACOSOG Z-0360 study evaluating patients with head/neck squamous cell cancer.³

In addition to the institutional study of head and neck (oral squamous cell carcinoma), two additional Phase III studies and one Phase II study were presented and published in peer-reviewed journals in support of the safety and efficacy of *technetium Tc 99m tilmanocept* in lymphatic mapping of patients with breast cancer and melanoma.⁴⁻⁷

The following enclosures are submitted in support of the above proposed changes:

1. Lymphoseek[®] (technetium Tc 99m tilmanocept) injection Prescribing Information. Navidea Biopharmaceuticals. September 2014.
(<http://www.lymphoseek.com/assets/pdfs/Lymphoseek%20Package%20Insert%20-%20October%202014.pdf>)
2. Agrawal A, Civantos F, et al. [^{99m}Tc]Tilmanocept Accurately Detects Sentinel Lymph Nodes and Predicts Node Pathology Status in Patients with Oral Squamous Cell Carcinoma of the Head and Neck: Results of a Phase III Multi-institutional Trial. *Ann Surg Oncol.* **2015**;22:3708-3715.
(http://annsurgoncol.org/journals/abstract.html?v=22&j=10434&i=11&a=4382_10.1245_s10434-015-4382-x&doi=)
3. Civantos FJ, Agrawal A, Lai SY. Comparison of false negative rates and overall accuracy of sentinel lymph node biopsy in phase 3 ^{99m}Tc-tilmanocept vs ACOSOG Z-0360 ^{99m}Tc-sulfur colloid in head/neck squamous cell cancer. In: Society of nuclear medicine and molecular imaging annual meeting. 11 Jun 2013, Vancouver.
4. Marcinow AM, Hall N, Byrum E, Teknos TN, Old MO, Agrawal A. Use of a novel receptor-targeted (CD206) radiotracer, ^{99m}Tc-tilmanocept, and SPECT/CT for sentinel lymph node detection in oral cavity squamous cell carcinoma: initial institutional report in an ongoing phase 3 study. *JAMA Otolaryngol.* **2013**;139:895-902.
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4301415/>)
5. Sondak VK, et al. Combined Analysis of Phase III Trials Evaluating [^{99m}Tc]Tilmanocept and Vital Blue Dye for Identification of Sentinel Lymph Nodes in Clinically Node-Negative Cutaneous Melanoma. *Ann Surg Oncol.* **2013**;20:680-8. (http://annsurgoncol.org/journals/abstract.html?v=20&j=10434&i=2&a=2612_10.1245_s10434-012-2612-z&doi=)
6. Wallace AM, et al. Comparative Evaluation of [^{99m}Tc]Tilmanocept for Sentinel Lymph Node Mapping in Breast Cancer Patients: Results of Two Phase 3 Trials. *Ann Surg Oncol.* **2013**;20:2590-2599.
(http://annsurgoncol.org/journals/abstract.html?v=20&j=10434&i=8&a=2887_10.1245_s10434-013-2887-8&doi=)
7. Leong S, et al. A Phase 2 Study of [^{99m}Tc]Tilmanocept in the Detection of Sentinel Lymph Nodes in Melanoma and Breast Cancer. *Ann Surg Oncol.* **2011**;18(4):961-969.
(http://annsurgoncol.org/journals/abstract.html?v=18&j=10434&i=4&a=1524_10.1245_s10434-010-1524-z&doi=)

Thank you for considering this request. Below is my information, please contact me should you have any questions regarding the content of this letter.

Sincerely,

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