

NCCN Adjuvant Breast Cancer Submission Cover Letter

Date: May 17, 2013

Submission Request c/o Joan McClure
National Comprehensive Cancer Network
500 Old York Road, Suite 250
Jenkintown, PA 19046

RE: Clinical Evidence in Support of the Use of Toremifene for Breast Cancer in the Adjuvant Setting

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Date of request: May 17, 2013
NCCN Guidelines Panel: Breast Cancer

Dear Guidelines Panel,

On behalf of ProStrakan Group, I respectfully request the NCCN Breast Cancer Guidelines Panel to review the enclosed data for the use of toremifene citrate (Fareston®) in the adjuvant management of patients with hormone-receptor-positive breast cancer.

Specific changes: As a result of the information provided in this letter and the accompanying documentation, we are requesting a change to the adjuvant endocrine therapy section of the guidelines (BINV-J).

We are also requesting an expansion of the footnote in the adjuvant treatment algorithm and discussion section to include information regarding the lack of interaction of toremifene with CYP2D6 inhibitors such as selective serotonin reuptake inhibitors (SSRIs) and to specify that patients taking concomitant medications that inhibit cytochrome P-450 2D6 (CYP2D6) may consider toremifene when clinically appropriate.

FDA status: Fareston® (toremifene citrate) has not been approved in the United States for adjuvant treatment of patients with breast cancer.

Rationale for recommended changes: The efficacy and safety of toremifene in the adjuvant setting have been demonstrated in several published studies. Furthermore, the comparable mechanisms of action and clinical activity of toremifene and tamoxifen have been acknowledged in several clinical studies of the use of toremifene as an alternative to tamoxifen for adjuvant treatment of breast cancer.

Although they have similar efficacy and safety profiles, a key difference between toremifene and tamoxifen is that they are metabolized by different hepatic enzymes, and this difference may impact treatment decisions. In brief, toremifene is believed to be active in its parent form and is mainly metabolized in the liver by CYP3A4 enzymes. In contrast, tamoxifen requires metabolism by CYP2D6

enzymes in order to be converted to its active metabolites. There are data demonstrating that potent CYP2D6 inhibitors, such as certain SSRIs, may affect the metabolism of tamoxifen but not that of toremifene.

Supporting literature: This request to amend the NCCN treatment guidelines to include toremifene as an option for the adjuvant treatment of estrogen-receptor–positive/progesterone-receptor–positive breast cancer is based on several key studies that are briefly described in the accompanying synopsis (the full list of supporting articles is in the synopsis document).

1. Gu R, Jia W, Zeng Y, et al. A comparison of survival outcomes and side effects of toremifene or tamoxifen therapy in premenopausal estrogen and progesterone receptor positive breast cancer patients: a retrospective cohort study. *BMC Cancer*. 2012;12:161.
2. Holli K, Valavaara R, Blanco G, et al. Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. Finnish Breast Cancer Group. *J Clin Oncol*. 2000;18(20):3487-3494.
3. International Breast Cancer Study Group, Paganì O, Gelber S, et al. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. *Ann Oncol*. 2004;15(12):1749-1759.
4. Kim J, Dalton JT, Veverka KA. Relationship of CYP2D6 status and toremifene metabolism. *J Clin Oncol*. 2011; 29(suppl); abstract e13068.
5. Kim J, Coss CC, Barrett CM, et al. Role and pharmacologic significance of cytochrome P-450 2D6 in oxidative metabolism of toremifene and tamoxifen. *Int J Cancer*. 2013;132(6):1475-1485.
6. Kimura M, Tominaga T, Kimijima I, et al. Phase III randomized trial of toremifene versus tamoxifen for Japanese postmenopausal patients with early breast cancer. *Breast Cancer*. 2012 Sep 12.
7. Lewis JD, Chagpar AB, Shaughnessy EA, Nurko J, McMasters K, Edwards MJ. Excellent outcomes with adjuvant toremifene or tamoxifen in early stage breast cancer. *Cancer*. 2010;116(10):2307-2315.

We appreciate the opportunity to provide this additional information for consideration by the NCCN Breast Cancer Panel. If you have any questions or require additional information, please do not hesitate to contact me at 908-375-7902 or via e-mail at deborah.braccia@prostrakan.com. Thank you for your time and consideration.

Sincerely,

Deborah Braccia, PhD, MPA

Enclosures:

Table of proposed changes

Synopsis

Copies of referenced literature