Submitted by:
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NCCN Guidelines Panel: Breast Cancer Panel (August 2020)

On behalf of the public, I respectfully request the NCCN Breast Cancer Panel to review the enclosed data for inclusion of Estrogen receptor alpha-36 (ER-α36) testing of all breast cancer tumors (initial presentation and recurrences) in addition to current ER-α66 testing, as a prerequisite to recommendation and/or administration of tamoxifen, in order to consider exclusion of tamoxifen from endocrine therapy in ER-α36 positive breast cancer patients to reduce tamoxifen-mediated metastasis, with the inclusion of ER-α36 testing to be made to all NCCN Guidelines for Breast Cancer (including but not limited to Breast Cancer Risk Reduction Guidelines and NCCN Evidence Blocks for Breast Cancer) in each place where reference is made to tamoxifen in such documents.

Specific Changes: Recommend ER-α36 testing of all breast cancer tumors (initial presentation and recurrences) in addition to current ER-α66 testing, as a prerequisite to recommendation or exclusion of tamoxifen therapy in light of potential for increased risk of metastases in ER-α36 positive breast cancer patients.

FDA Clearance: Tamoxifen has been approved by the FDA for breast cancer.

Rationale: Multiple studies have indicated that tamoxifen "directly binds and activates ER-α36 to enhance the stemness and metastasis of breast cancer cells"; that tamoxifen "promotes breast cancer metastasis via activation of ER-α36"; that "ER-α36 expression increased significantly after a low dose tamoxifen exposure in MCF-7 cell line" and that "this upregulation was previously associated with a decreased sensitivity to tamoxifen and enhanced proliferative, migratory, and invasive abilities of breast cancer cells"; that "experimental results provided support and explanations to clinical studies wherein a high ER-α36 expression in tumors treated with tamoxifen was significantly associated with a poor prognosis and an increased rate of metastases"; and have recommended that "tamoxifen should be excluded from endocrine therapy in ER-α36 positive breast cancer patients to reduce tamoxifen-mediated metastasis through ER-α36 activation" since "tamoxifen does not act as a drug for cancer treatment but serves as an ER-α36 agonist, triggering proliferation, migration and invasion", noting that "the majority of ER+ tumors also express high levels of ER-α36" and that ER-α36 "is expressed in about half of breast tumors, independently of ER+/ER- status."

The following articles, which include data from clinical studies, are submitted in support of this proposed change.

1. Wang Q, Jiang J, Ying G, Xie XQ, Zhang X, Xu W, Zhang X, Song E, Bu H, Ping YF, Yao XH, Wang B, Xu S, Yan ZX, Tai Y, Hu B, Qi X, Wang YX, He ZC, Wang Y, Wang JM, Cui YH, Chen F, Meng K, Wang Z, Bian XW. Tamoxifen enhances stemness and promotes metastasis of ERα36+ breast cancer by upregulating ALDH1A1 in cancer cells. Cell Res. 2018 Mar;28(3):336-358. doi: 10.1038/cr.2018.15. Epub 2018 Feb 2. PMID: 29393296; PMCID: PMC5835774.
   (Accessible at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5835774/)
2. Shi L, Dong B, Li Z, Lu Y, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, Wang Z, Xie Y. Expression of ER-{alpha}36, a novel variant of estrogen receptor {alpha}, and resistance to

tamoxifen treatment in breast cancer. J Clin Oncol. 2009 Jul 20;27(21):3423-9. doi: 10.1200/JCO.2008.17.2254. Epub 2009 Jun 1. PMID: 19487384; PMCID: PMC2717750. (Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2717750/)

3. Chamard-Jovenin, C., Jung, A.C., Chesnel, A. et al. From ERα66 to ERα36: a generic method for validating a prognosis marker of breast tumor progression. BMC Syst Biol 9, 28 (2015) doi:10.1186/s12918-015-0178-7
(Accessible at https://bmcsystbiol.biomedcentral.com/articles/10.1186/s12918-015-0178-7)
4. Thiebaut C, Chesnel A, Merlin JL, Chesnel M, Leroux A, Harlé A, Dumond H. Dual Epigenetic Regulation of ERα36 Expression in Breast Cancer Cells. Int J Mol Sci. 2019 May 29;20(11):2637. doi: 10.3390/ijms20112637. PMID: 31146345; PMCID: PMC6600239. (Accessible at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6600239/)

Sincerely,

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