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NCCN Guidelines Panel: Breast Cancer

On behalf of TerSera Therapeutics, I respectfully request the NCCN Breast Cancer Panel to review the enclosed data and the following recommendations.

- 1) Clarify that goserelin is the only FDA-approved LHRH agonist for the management of breast cancer in the Adjuvant Endocrine Therapy discussion. Clarify that leuprolide is not FDA-approved for breast cancer.
 - *Specific Changes:* Goserelin is the only LHRH agonist available in the United States that is FDA-approved for patients with breast cancer.
 - *FDA Clearance:* Zoladex® (goserelin acetate implant) 3.6 mg is FDA-approved for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.¹
 - *Rationale:* The GnRH agonist leuprolide acetate (Lupron Depot®) is not FDA-approved for use in patients with breast cancer.^{2,3}
 - *Supporting References:*
 1. ZOLADEX 3.6 mg Prescribing Information. www.tersera.com/prescribing-information
 2. LUPRON 3.75 mg Prescribing Information.
 3. LUPRON 11.25 mg Prescribing Information.
- 2) Include a discussion of the volume of published data and clinical trials supporting the administration of goserelin for ovarian suppression in the Adjuvant Endocrine Therapy discussion.
 - *Specific Changes:* Goserelin was the only available drug option to achieve ovarian suppression for premenopausal patients with breast cancer enrolled in the pivotal clinical trials PALOMA3 (palbociclib) and MONALEESA-7 (ribociclib).^{4,5} In addition, goserelin is included in the protocols of approximately 75 clinical trials in the national database, including 40 that are planned or ongoing.⁵ Furthermore, there are 379 citations of goserelin and breast cancer in the literature since 1995, the year in which goserelin was approved for breast cancer.⁶
 - *FDA Clearance:* Zoladex® (goserelin acetate implant) 3.6 mg is FDA-approved for the monthly administration for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.¹

- *Rationale:* Based on the FDA approval of goserelin for breast cancer and its established benefit, a large number of clinical trials have included goserelin as the agent of choice for ovarian suppression, including PALOMA3 and MONALEESA-7.^{4,5} It is well established that due to basic pharmacology, the administration of aromatase inhibitors in premenopausal women dictates the need for ovarian suppression with a GnRH agonist.⁷
 - *Supporting References:*
 1. ZOLADEX 3.6 mg Prescribing Information. www.tersera.com/prescribing-information
 4. Tiner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015;373:209-219.
 5. National Institutes of Health. Clinicaltrials.gov. Available at: www.clinicaltrials.gov. Accessed June 27, 2017.
 6. Embase® Search Strategy. May 26, 2017.
 7. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med* 2003;348:2431-2442.
- 3) Include a discussion of goserelin versus oophorectomy as ovarian suppression in premenopausal patients with breast cancer in the Adjuvant Endocrine Therapy discussion.
- *Specific Changes:* Goserelin has demonstrated efficacy equivalent to oophorectomy in premenopausal patients with breast cancer. As a result, clinicians should strongly consider ovarian suppression with goserelin versus oophorectomy in such patients.
 - *FDA Clearance:* Zoladex® (goserelin acetate implant) 3.6 mg is FDA-approved for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.¹
 - *Rationale:* Oophorectomy is an irreversible and permanent procedure. Goserelin provides an alternative to oophorectomy. Taylor et al compared clinical outcomes of premenopausal women with metastatic breast cancer randomly assigned to management with surgical ovariectomy versus monthly goserelin.⁸ Failure-free survival (FFS) and overall survival (OS) were not significantly different between the treatment groups.
 - *Supporting References:*
 1. ZOLADEX 3.6 mg Prescribing Information. www.tersera.com/prescribing-information
 8. Taylor CW, Green S, Dalton WS, et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: An intergroup study. *J Clin Oncol* 1998;16:994-999.
- 4) Include a discussion of potential long-term negative consequences of oophorectomy as ovarian suppression in premenopausal patients with breast cancer in the Adjuvant Endocrine Therapy discussion.
- *Specific Changes:* Goserelin has demonstrated efficacy equivalent to oophorectomy in premenopausal patients with breast cancer. The long-term negative consequences of an oophorectomy can be significant, particularly in younger females. As a result, clinicians should discuss the risks and strongly consider ovarian suppression with goserelin versus oophorectomy in such patients.
 - *FDA Clearance:* Zoladex is FDA-approved for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.¹

- *Rationale:* Oophorectomy before natural menopause results in an abrupt reduction in endogenous estrogen and androgen production.^{9,10} Data suggests that preserving ovarian function may be associated with a lower risk of developing coronary heart disease (CHD), cognitive impairment, and osteoporosis.¹⁰⁻¹² Results from a landmark analysis demonstrated that increased total mortality risk was associated with the age of oophorectomy: HR at ≤ 40 years of age was 1.12 (95% CI 1.04–1.21).¹³ Similarly, results from a large prospective cohort study demonstrated the risk of CHD death was increased in patients who underwent an oophorectomy at < 50 years of age, HR was 1.29 (95% CI 1.01–1.64).¹⁴ A meta-analysis of 18 studies indicated that women who underwent oophorectomy were significantly more likely to develop cardiovascular disease (CVD) compared with premenopausal age-matched women (relative risk [RR] was 2.62 [95% CI 2.05–3.35]).⁹ Furthermore, a well-established risk factor for the development of osteoporosis is oophorectomy before the age of 45 years.¹²

- *Supporting References:*

1. ZOLADEX 3.6 mg Prescribing Information. www.tersera.com/prescribing-information
9. Rodriguez M, Shoupe D. Surgical menopause. *Endocrinol Metab Clin N Am* 2015;44:531-542.
10. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the Nurses' Health Study. *Obstet Gynecol* 2009;113:1027-1037.
11. Rocca WA, Grossardt B, Shuster LT, et al. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. *Neurodegenerative Dis* 2012;10:175-178.
12. Shuster LT, Bostout BS, Grossardt BR, et al. Prophylactic oophorectomy in pre-menopausal women and long term health – a review. *Menopause Int* 2008;14:111-116.
13. Gierach GL, Pfeiffer RM, Patel DA, et al. Long-term overall and disease-specific mortality associated with benign gynecologic surgery performed at different ages. *Menopause* 2014;21:592-601.
14. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the Nurses' Health Study. *Obstet Gynecol* 2013;121:709-716.

5) Include discussion of literature on goserelin administration every 3 months in breast cancer.

- *Specific Changes:* Addition of literature on goserelin 10.8 mg every 3 months compared to 3.6 mg every month that has demonstrated non-inferiority in estradiol levels and outcome measures.
- *FDA Clearance:* Zoladex® (goserelin acetate implant) 3.6 mg is FDA-approved for the monthly administration for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.¹
- *Rationale:* The 10.8 mg formulation is not indicated in women. However, there is published data demonstrating that 10.8 mg every 3 months had similar outcomes as 3.6 mg every month in patients with breast cancer.¹⁵⁻¹⁷ Noguchi et al compared goserelin 10.8 mg subcutaneous every 3 months with goserelin 3.6 mg subcutaneous every 1 month in premenopausal patients with estrogen receptor (ER)-positive breast cancer.¹⁶ Goserelin 10.8 mg every 3 months met the criteria for non-inferiority compared with goserelin 3.6 mg monthly in terms of proportion of patients who were progression-free at 24 weeks. A pharmacokinetic study conducted by Masuda et al reported non-inferiority in estradiol levels between goserelin 10.8 mg and goserelin 3.6 mg.¹⁷



- *Supporting References:*

1. ZOLADEX 3.6 mg Prescribing Information. www.tersera.com/prescribing-information
15. ZOLADEX 10.8 mg Prescribing Information. www.tersera.com/prescribing-information
16. Noguchi S, Kim HJ, Jesena A, et al. Phase 3, open-label, randomized study comparing 3-monthly with monthly goserelin in pre-menopausal women with estrogen receptor-positive advanced breast cancer. *Breast Cancer* 2016;23:771-779.
17. Masuda N, Iwata H, Rai Y, et al. Monthly versus 3-monthly goserelin acetate treatment in pre-menopausal patients with estrogen receptor-positive early breast cancer. *Breast Cancer Res Treat* 2011;126:443-451.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Masuda N", written in a cursive style.