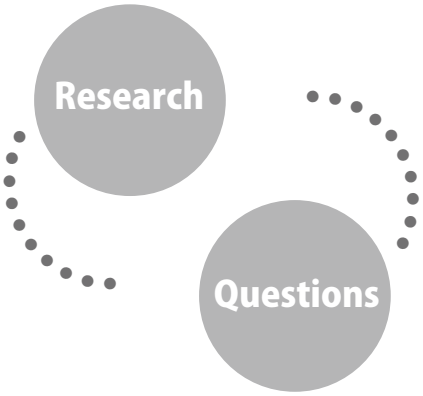
## "Practice Guidelines for Breast Cancer"

**～ A Comparison between U.S. and Japan ～**

(U.S.: as of 2007, Japan: according to "Practice Guideline for Breast Cancer"(2005) published by the Japanese Breast Cancer Society)

# 3. Chemotherapy




National Comprehensive Cancer Network (NCCN)
Nonprofit Organization Japan Comprehensive Cancer Network, Breast (JCCNB)

Workshop on Clinical Cancer Research Project organized by
The Ministry of Health, Labour and Welfare, Japan

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**NCCN Categories of Consensus**

< Category **I** > There is uniform NCCN consenus, based on high-level evidence, that the recommendation is appropriate.
< Category **IIA** > There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.
< Category **IIB** > There is nonuniform NCCN consensus, (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.
< Category **III** > There is major NCCN disagreement that the recommendation is appropriate

## Basic Treatment Principles

### 1 What basic principles should be adopted to choose the drug therapy in the primary treatment of breast cancer?

**Japan** ＜ Recommended Grade：**A** ＞

It is recommended to choose the therapy based on the status of hormone receptors and HER-2, and the risk of recurrence after obtaining the informed consent from patients with discussion of the expected benefits (decrease in recurrence and death rate) and adverse events from all possible therapeutic options.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

The current version of the NCCN Guidelines first recognizes subsets of patients with early breast cancer of the usual histologies based upon responsiveness to endocrine therapy and trastuzumab (ie, hormone receptor status, HER2 status) . Patients are then further stratified based upon risk for recurrence of disease based upon anatomic and pathologic characteristics (ie, tumor grade, tumor size, axillary lymph node status, angiolymphatic invasion)

### 2 What basic principles should be adopted to choose the drug therapy after metastasis or recurrence?

**Japan** ＜ Recommended Grade：**A** ＞

It is recommended to establish the best treatment objectives in consideration of patient' s value after assessing the patient' s prognostic and predictive factors (sites and extent of metastasis, hormone sensitivity, status of HER-2, disease-free interval, age and menopause status).

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

The current version of the NCCN Guidelines first recognizes subsets of patients based upon presence or absence of bone disease, then on biological markers of responsiveness to endocrine therapy and trastuzumab (ie, hormone receptor status, HER2 status)

### 3 Does preoperative hormone therapy increase the rate of breast conservation in postmenopausal hormone-sensitive primary breast cancer? Is there any difference in prognosis between preoperative and postoperative hormone therapy?

**Japan**

＜ Recommended Grade：**B** ＞

Preoperative hormone therapy improves the breast-conserving rate.

＜ Recommended Grade：**C** ＞

There are no evidences suggesting that preoperative hormone therapy yields the equivalent prognosis to postoperative hormone therapy.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Several randomized trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with estrogen receptor-positive breast cancer. These studies have generally compared the rates of objective response and rates of breast-conserving surgery among treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently demonstrate that the use of either anastrozole or letrozole alone provides superior rates of breast-conserving surgery and usually objective response.[i],[ii] On the basis of these trials, preoperative endocrine therapy with an aromatase inhibitor is an option in the treatment of postmenopausal women with hormone receptor-positive disease.[i]. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol. 2005;23:5108-5116. [ii]. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 2001;19:3808-3816.

Not addressed directly in the guidelines.

### 4 Does the ovarian function-suppressing therapy improve the prognosis in patients with premenopausal early-stage breast cancer?

**Japan** ＜ Recommended Grade：**A** ＞

The ovarian function-suppressing therapy improves the prognosis in patients with premenopausal early-stage breast cancer.

**U.S.** ＜ NCCN Categories of Consensus ：**IIB** ＞

Premenopausal patients who are hormone receptor positive should be treated with tamoxifen with or without ovarian ablation.

## 5 Are hormone therapy and chemotherapy equivalent in prognosis for premenopausal hormone-sensitive early-stage breast cancer?

**Japan** ＜Recommended Grade：**B**＞

There are no marked differences in prognosis between hormone therapy (LH-RH analogue ± tamoxifen) and chemotherapy (CMF, AC, FEC and FAC) in premenopausal hormone-sensitive early-stage breast cancer.

**U.S.** ＜NCCN Categories of Consensus：**IIA**＞

Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit from ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain..

## 6 Is the ovarian function-suppression after chemotherapy beneficial in premenopausal hormone-sensitive early-stage breast cancer?

**Japan** ＜Recommended Grade：**B**＞

It is likely to improve prognosis by adding ovarian function-suppressing therapy after chemotherapy. It is expected to be more beneficial especially for patients forty years old or younger

**U.S.** ＜NCCN Categories of Consensus：**IIA**＞

Premenopausal patients who are hormone receptor positive should be treated with tamoxifen with or without ovarian ablation. Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit from ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

## 7 Is postoperative tamoxifen more beneficial than no treatment in hormone-sensitive early-stage breast cancer?

**Japan** ＜Recommended Grade：**A**＞

Postoperative 5-year treatment with tamoxifen is beneficial in hormone-sensitive early-stage breast cancer.

**U.S.** ＜NCCN Categories of Consensus：**I**＞

In women with estrogen receptor-positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or axillary lymph node status. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687-1717.

## 8 Which is more effective, tamoxifen or an aromatase inhibitor, in postmenopausal hormone-sensitive early-stage breast cancer?

**Japan** ＜Recommended Grade：**A**＞

Five-year treatment with aromatase inhibitor (anastrozole, letrozole) prolongs the disease-free interval more than 5-year treatment with tamoxifen, but the effect on the overall survival is not clear.

**U.S.** ＜NCCN Categories of Consensus：**I**＞

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2-3 years of tamoxifen, or as extended therapy following 4.5 -6 years of tamoxifen. The various studies are consistent in demonstrating that the use of a third generation aromatase inhibitor in postmenopausal women with hormone receptor-positive breast cancer lowers the risk of recurrence, including ipsilateral breast tumor recurrence, contralateral breast cancer, and distant metastatic disease, compared to tamoxifen alone when the aromatase inhibitor is used as initial adjuvant therapy, sequential therapy, or extended therapy. The current version of the guideline recommends that postmenopausal women with early breast cancer receive an aromatase inhibitor as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy in those situations where endocrine therapy is to be utilized.

## 9 In the postoperative treatment of postmenopausal hormone-sensitive early-stage breast cancer, does an aromatase inhibitor changed from tamoxifen improve prognosis?

**Japan** ＜ Recommended Grade：**A** ＞

The disease-free interval can be prolonged by switching to an aromatase inhibitor (exemestane, anastrozole) after 2-3 years of tamoxifen to complete a total of 5 years of endocrine therapy.

**U.S.** ＜ NCCN Categories of Consensus ：**I** ＞

The results from two prospective, randomized clinical trials have provided early evidence of an overall survival benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole or exemestane when compared with tamoxifen as the only endocrine therapy.[i],[ii] In addition, the National Cancer Institute Canada Clinical Trials Group (NCIC CTG) MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in women with axillary lymph node-positive (but not lymph node-negative), estrogen receptor-positive breast cancer.[iii] [i]. Coombes RC, Paridaens R, Jassem J, et al. First mature analysis of the Intergroup exemestane study [meeting abstract]. J Clin Oncol. 2006;24:18s(June 20 suppl). Abstract LBA527[ii]. Kaufmann M, Jonat W, Hilfrich J, et al. Survival benefit of switching to anastrozole after 2 years' treatment with tamoxifen versus continued tamoxifen therapy: The ARNO 95 study [meeting abstract]. J Clin Oncol. 2006;24:18s(June 20 suppl). Abstract 547.[iii]. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 2005;97:1262-1271.

## 10 What therapy is recommended after postoperative 5-year treatment with tamoxifen for hormone -sensitive early-stage breast cancer?

**Japan** ＜ Recommended Grade：**B** ＞

Sequential aromatase inhibitors (letrozole, anastrozole and exemestane) can be considered for patients with postmenopausal hormone-sensitive early-stage breast cancer who have received 5-year postoperative treatment with tamoxifen.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Breast International Group (BIG) 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. An early analysis compared tamoxifen alone versus letrozole alone, including those patients in the sequential arms during their first two years of treatment only.[i] With 8,010 women included in the analysis, disease-free survival was superior in the letrozole treated women (hazard rate 0.81; 95% CI 0.70 – 0.93; log rank P=0.003). No interaction between progesterone receptor expression and benefit was observed. No difference in overall survival has been observed.

## 11 Which is more effective concurrent hormone therapy and chemotherapy or sequential administration of those for the postoperative treatment of hormone-sensitive early-stage breast cancer?

**Japan** ＜ Recommended Grade：**B** ＞

Postoperative chemotherapy (anthracyclines) followed by endocrine therapy (tamoxifen) is more preferred than concurrent therapy for the hormone-sensitive early-stage breast cancer.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Hormonal therapy is generally given followng completion of chemotherapy.

## 12 Is postoperative hormone therapy beneficial after breast-conserving surgery in patients with non- infiltrative ductal cancer?

**Japan** ＜ Recommended Grade：**C** ＞

Tamoxifen may reduce the risk of recurrence in the ipsilateral breast and development of contralateral disease. Indication of tamoxifen to this group should be carefully examined in consideration of toxicities.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

the NSABP B-24 trial found a benefit from tamoxifen for women with DCIS after treatment with breast conservation surgery and radiation therapy. In that study, women with DCIS who were treated with breast-conserving therapy were randomized to receive placebo or tamoxifen. The women treated with tamoxifen had a 5% absolute reduction in recurrence risk and a 37% reduction in relative risk. The women receiving tamoxifen had an 8.2% total incidence of breast cancer (4.1% invasive and 4.2% noninvasive) compared with a 13.4% incidence of breast cancer (7.2% invasive and 6.2% noninvasive) in the placebo-treated women at a median follow-up of 74 months. The cumulative incidence of invasive breast cancer at 5 years in the ipsilateral breast was 4.2% and 2.1% in women receiving placebo and tamoxifen, respectively, and in the contralateral breast, 2.3% and 1.8% in the placebo and tamoxifen groups, respectively). A retrospective analysis of estrogen receptor expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms of reduction of risk for the development of both ipsilateral and contralateral breast cancer following breast-conserving therapy. [i] Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet. 1999;353:1993-2000. [ii]. Allred D, Bryant J, Land S, et al. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24 [meeting abstract]. Breast Cancer Res Treat. 2002;76(suppl 1):Abstract 30.

## 13 Which is more effective concurrent administration of hormone therapy and chemotherapy or sequential administration of those in metastatic or recurrent breast cancer?

**Japan** ＜Recommended Grade：**B**＞

It has not been demonstrated that concurrent administration of hormone therapy and chemotherapy is more effective than sequential administration in metastatic or recurrent breast cancer. Sequential hormone therapy and chemotherapy is recommended.

**U.S.** ＜NCCN Categories of Consensus：**IIA**＞

The treatment of systemic recurrence of breast cancer prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable. Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at the time of disease progression. Therefore, women whose breast cancers respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at the time of disease progression. Women with hormone receptor-positive tumors that are refractory to endocrine therapy, should receive chemotherapy

## 14 What therapy is recommended as the first and second-line hormone therapy for premenopausal metastatic or recurrent breast cancer?

**Japan**

＜Recommended Grade：**A**＞

Combination therapy with LH-RH analog and tamoxifen is recommended as the first-line hormonal therapy for premenopausal hormone-sensitive metastatic or recurrent breast cancer.

＜Recommended Grade：**C**＞

Combination therapy with LH-RH analog and aromatase inhibitor could be beneficial as the second-line therapy although it is not scientifically proven.

**U.S.**

＜NCCN Categories of Consensus：**IIA**＞

In premenopausal women with previous antiestrogen therapy who are within 1 year of antiestrogen exposure, the preferred second-line therapy is either surgical or radiotherapeutic oophorectomy or leuteinizing hormone-releasing hormone (LHRH) agonists with endocrine therapy as for postmenopausal women. In premenopausal women without previous exposure to an antiestrogen, initial treatment with an antiestrogen with or without a LHRH agonist or ovarian ablation is preferred. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteninizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 2001;19:343-353.

＜NCCN Categories of Consensus：**IIA**＞

In premenopausal women with previous antiestrogen therapy who are within 1 year of antiestrogen exposure, the preferred second-line therapy is either surgical or radiotherapeutic oophorectomy or leuteinizing hormone-releasing hormone (LHRH) agonists with endocrine therapy as for postmenopausal women. In premenopausal women without previous exposure to an antiestrogen, initial treatment with an antiestrogen with or without a LHRH agonist or ovarian ablation is preferred. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteninizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 2001;19:343-353.

## 15 What is the recommended first-line hormone therapy for postmenopausal metastatic or recurrent breast cancer?

**Japan** ＜Recommended Grade：**A**＞

An aromatase inhibitor (anastrozole, letrozole or exemestane) is recommended as the first-line therapy for postmenopausal hormone-sensitive metastatic or recurrent breast cancer.

**U.S.** ＜NCCN Categories of Consensus：**I**＞

In postmenopausal women with previous antiestrogen therapy and who are within one year of antiestrogen exposure, recent evidence supports the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.[i],[ii] For postmenopausal women who are antiestrogen naive or who are more than 1 year from previous antiestrogen therapy, the aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.[iii]-,[iv],[v],[vi],[vii] Therefore, either tamoxifen or an aromatase inhibitor is an appropriate option in this setting.[i]. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol. 2001;19:3357-3366.[ii]. Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. Cancer. 1998;83:1142-1152.[iii]. Bonneterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol. 2000;18:3748-3757.[iv]. Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol. 2001;19:2596-2606.[v]. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal

women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol. 2000;18:3758-3767.[vi]. Vergote I, Bonneterre J, Thurlimann B, et al. Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. Eur J Cancer. 2000;36 (suppl 4):S84-85.[vii]. Paridaens R, Therasse P, Dirix L, et al. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) - A randomized phase III trial of the EORTC Breast Group [meeting abstract]. J Clin Oncol. 2004;22:14S (July 15 suppl). Abstract 515.

## 16 What is the recommended second-line hormone therapy for postmenopausal metastatic or recurrent breast cancer?

**Japan**

＜推奨グレード：**A**＞

In the tamoxifen-resistant postmenopausal metastatic or recurrent breast cancer, an aromatase inhibitor is recommended as the second-line therapy.

＜推奨グレード：**B**＞

In the aromatase inhibitor-resistant postmenopausal metastatic or recurrent breast cancer, either tamoxifen or an aromatase inhibitor with a different antitumor mechanism is recommended.

**U.S.**

＜ NCCN Categories of Consensus ：**IIA** ＞

The antiestrogen fulvestrant recently became available for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer previously treated with an antiestrogen. Fulvestrant lacks the estrogen agonistic activity of tamoxifen and is well tolerated as a single monthly gluteal intramuscular injection. Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous endocrine therapy,[i],[ii] and a recent reanalysis of these studies suggests a longer duration of response favoring fulvestrant.[iii]Endocrine therapies in postmenopausal women include selective, nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); pure anti-estrogens (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). In premenopausal women, therapies include LHRH agonists (goserelin and luprolide); surgical or radiotherapeutic oophorectomy; progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy. [i]. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol. 2002;20:3386-3395.[ii]. Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol. 2002;20:3396-3403.[iii]. Robertson JF, Osborne CK, Howell A, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. Cancer. 2003;98:229-238.

＜ NCCN Categories of Consensus ：**IIA** ＞

A retrospective analysis of tumor blocks collected in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.[i] However, given the favorable toxicity profile of the available endocrine therapies, the Panel recommends the use of adjuvant endocrine therapy in the majority of women with hormone receptor-positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor. [i]. Dowsett M, Allred DC on Behalf of the TransATAC Investigators. Relationship between quantitative ER and PgR expression and HER2 status with recurrence in the ATAC trial. San Antonio Breast Cancer Symposium. 2006; Abstract 48.

## 17 Is it effective to use hormone therapy for hormone receptor-negative breast cancer?

**Japan** ＜ Recommended Grade：**D** ＞

Hormone therapy is not effective in hormone receptor-negative breast cancer in either adjuvant setting or metastatic/recurrent cases.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Women with hormone receptor-negative disease or hormone receptor-positive disease that was refractory to prior endocrine therapy if disease is characterized as bone or soft tissue only or asymptomatic visceral may benefit from a trial of hormonal therapy.

## 18 Is it useful to consider progesterone receptor status when selecting a hormonal agent?

**Japan** ＜ Recommended Grade：**C** ＞

There are no sufficient evidences to support hormone therapy based on progesterone receptor status.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Patients with invasive breast cancers that are estrogen or progesterone receptor-positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether or not adjuvant chemotherapy is to be administered. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet. 1998;351:1451-1467.

## 19 Is hormone replacement therapy recommended for postoperative early-stage breast cancer patients?

**Japan** ＜ Recommended Grade：**D** ＞

Hormone replacement therapy (HRT) should not be implemented in postoperative breast cancer patients.

**U.S.**

Not addressed

## 20 Is it beneficial to use aromatase inhibitor monotherapy for premenopausal breast cancer patients?

**Japan** ＜ Recommended Grade：**D** ＞

Aromatase inhibitor alone should not be used for premenopausal breast cancer patients.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

The aromatase inhibitors are associated with the development of benign ovarian pathology and do not adequately suppress ovarian estrogen synthesis in women with functioning ovaries, and premenopausal women should not be given therapy with an aromatase inhibitor outside the confines of a clinical trial. Women who are premenopausal at the time of diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries in the absence of menses. Serial assessment of circulating LH, FSH, and estradiol to assure a true postmenopausal status is mandatory if this subset of women are to be considered for therapy with an aromatase inhibitor[i],[ii] [i]. Braverman AS, Sawhney H, Tendler A, et al. Pre-menopausal serum estradiol (E2) levels may persist after chemotherapy (CT)-induced amenorrhea in breast cancer (BC) [meeting abstract]. Proc Am Soc Clin Oncol. 2002;21:Abstract 164.[ii]. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 2006;24:2444-2447.

# Treatment against HER-2-positive breast cancer

## 21 Is trastuzumab effective in HER-2-positive early-stage breast cancer?

**Japan** ＜ Recommended Grade：**B** ＞

Trastuzumab is effective in HER-2-positive early-stage breast cancer.

**U.S.** ＜ NCCN Categories of Consensus ：**I** ＞

Results of five randomized trials testing trastuzumab as adjuvant therapy were recently reported.i, ii, iii,iv In NSABP B-31 patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every three weeks followed by paclitaxel 4 cycles every three weeks or the same regimen with 52 weeks of trastuzumab commencing with the paclitaxel. In the North Central Cancer Treatment Group (NCCTG) N9831 trial, patients with HER2-positive breast cancer that was node-positive, or, if node-negative, with primary tumors greater than 1 cm in size if ER- and PR- negative or greater than 2 cm in size if ER- or PR-positive, were similarly randomized except that paclitaxel was given by a low dose weekly schedule for 12 weeks and a third arm delayed trastuzumab until the completion of paclitaxel. The B-31 and NCCTG N9831 trials were jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with the paclitaxel.[i] There were 3,351 patients included in the joint analysis performed at 2 years median follow-up. A 52% reduction in the risk of recurrence (hazard ratio 0.48; 95% CI 0.39-0.59; P<0.0001) and a 33% reduction in the risk of death (hazard ratio 0.67; 95% CI 0.48-0.93; log-rank P = 0.015) were documented. Similar significant effects on disease-free survival were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.[vii], A third trial (HERA) (N=5081) tested trastuzumab for one or for two years compared to none following all local therapy and a variety of standard chemotherapy regimens in patients with node-positive disease or node-negative disease with tumor ≥ 1 cm .ii At a median follow-up of one year, comparing one year versus not of trastuzumab, trastuzumab resulted in a 46% reduction in the risk of recurrence compared to no trastuzumab (hazard ratio 0.54; 95% CI 0.43-0.67; P < 0.0001), no difference in overall survival, and acceptable cardiac toxicity. The two year data indicate that 1-year of trastuzumab therapy is associated with an overall survival benefit when compared with observation (hazard ratio for risk of death=0.66; 95% CI, 0.47-0.91; P=0.0115). The Breast Cancer International Research Group (BCIRG) 006 study randomized 3,222 women with HER2-positive, node-positive or high-risk node negative breast cancer to AC followed by docetaxel, AC followed by docetaxel plus trastuzumab for one year, or carboplatin, docetaxel plus trastuzumab for one year.iii At 36 months of follow-up, patients receiving AC followed by docetaxel with trastuzumab (ACCèTH) had a hazard ratio for disease-free recurrence of 0.61 (95% CI, 0.48-0.76; P<0.0001) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (ACCèT). The hazard ratio for disease-free survival was 0.67 (95% CI, 0.54-0.83; P=0.0003) when patients in the carboplatin/docetaxel/ trastuzumab (TCH) containing arm were compared to patients in the control arm. No statistically significant difference in the hazard ratio for disease-free survival was observed between the two trastuzumab-containing arms. An overall survival advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (hazard ratio for AC-TH vs AC-T=0.59; 95% CI, 0.42-0.85; P=0.004; hazard ratio for TCH vs AC-T=0.66; 95% CI, 0.47-0.93; P=0.017). Cardiac toxicity was significantly lower in the TCH arm (8.6% patients with >10% relative decline in left ventricular ejection fraction) compared with the AC-TH arm (18%; P<0.0001); differences in cardiac toxicity between the TCH arm and the AC-T control arm (10%) were not significant. A fifth trial (FinHer) randomized 1010 women to either 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.iv Patients (N=232) with HER2-positive cancers that were either node-positive or node-negative and ≥ 2 cm and progesterone receptor- negative were further randomized to receive or not trastuzumab for 9 weeks during the vinorelbine or docetaxel

portions of the chemotherapy only. With a median follow-up of 3 years, the addition of trastuzumab was associated with a reduction in risk of recurrence (hazard ratio 0.42; 95% CI 0.21-0.83; P=0.01). No statistically significant differences in overall survival (hazard ratio 0.41; 95% CI 0.16 – 1.08; P=0.07) or cardiac toxicity were observed with the addition of trastuzumab. All of the adjuvant trials of trastuzumab demonstrate clinically significant improvements in disease-free survival. [i]. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353:1673-1684.. [ii]Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:1659-1672. [iii]Slamon D, Eiermann W, Robert N, et al. Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients : second interim efficacy analysis. San Antonio Breast Cancer Symposium. 2006; Abstract 52 . [iv]Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809-820. [v]Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23:7811-7819. [vi] Perez EA, Suman VJ, Davidson NE, et al. Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial [meeting abstract]. J Clin Oncol. 2005;23:16s(June 1 suppl). Abstract 556. [vii] Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomized controlled trial. Lancet. 2007:369:29-36.

## 22 Is trastuzumab effective in HER-2-positive metastatic or recurrent breast cancer?

**Japan** ＜ Recommended Grade：**A** ＞

Trastuzumab combined with chemotherapy is effective in HER-2-positive metastatic or recurrent breast cancer.

**U.S.** ＜ NCCN Categories of Consensus ：**I** ＞

Patients with tumors that are HER2-positive may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents, or the combination of capecitabine plus lapatinib for those refractory to therapy with an anthracycline, a taxane, and trastuzumab . The Panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 by FISH or 3+ by IHC. HER2 testing recommendations are described in the guideline. Patients with tumors IHC 0 or 1+ for HER2 or FISH not amplified have very low rates of HER2-targeted response, and therapy with trastuzumab or lapatinib is not warranted.

## 23 How should trastuzumab be administered in HER-2-positive metastatic or recurrent breast cancer?

**Japan**

＜ Recommended Grade：**B** ＞

Trastuzumab monotherapy is likely to be effective in HER-2-positive metastatic or recurrent breast cancer.

＜ Recommended Grade：**C** ＞

Trastuzumab combined with chemotherapy may be effecitve in HER-2-positive metastatic or recurrent breast cancer.

＜ Recommended Grade：**C** ＞

Continuation of trastuzumab may be beneficial in patients with disease progression on second-line therapy.

＜ Recommended Grade：**B** ＞

Every 3 weeks administration of trastuzumab is likely to be as effective as weekly administration.

**U.S.**

＜ NCCN Categories of Consensus ：**IIA** ＞

In patients with metastatic or recurrent breast cancer with HER2-positive tumors, trastuzumab as a single agenti, ii may be considered. [i]Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 1999;17:2639-2648.[ii] Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20:719-726

＜ NCCN Categories of Consensus ：**IIA** ＞

In patients with metastatic or recurrent breast cancer with HER2-positive tumors, trastuzumab in combination with selected chemotherapeutics may be considered. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783-792.

＜ NCCN Categories of Consensus ：**IIA** ＞

The value of continued trastuzumab following progression on first line-trastuzumab containing chemotherapy for metastatic breast cancer is unknown. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

＜ NCCN Categories of Consensus ：**IIA** ＞

The current guideline includes doses and schedules of representative chemotherapy single agents and regimens for use in combination with either trastuzumab or lapatinib for metastatic breast cancer

## 24 Is it reasonable to select type of chemotherapy or hormone therapy based on HER-2 status?

Japan ＜ Recommended Grade：**C** ＞

There are no sufficient evidences for the HER-2 status to predict the efficacy of chemotherapy or hormone therapy, but the efficacy of anthracycline may be predicted.

U.S. ＜ NCCN Categories of Consensus ：**IIA** ＞

Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive,i, ii, iii, iv has led to a footnote stating that anthracycline-based chemotherapy may be superior to non-anthracycline-containing regimens in the adjuvant treatment of such patients. [i] Paik S, Bryant J, Park C, et al. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. J Natl Cancer Inst. 1998;90:1361-1370. [ii]Paik S, Bryant J, Tan-Chiu E, et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Natl Cancer Inst. 2000;92:1991-1998. [iii] Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst. 1998;90:1346-1360 [iv]Pritchard KI, Shepherd LE, O'Malley FP, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med. 2006;354:2103-2111

# Chemotherapy

## 25 Is preoperative chemotherapy beneficial for patients with operable early-stage breast cancer?

Japan

＜ Recommended Grade：**A** ＞

Preoperative chemotherapy provides the equivalent survival benefit as postoperative chemotherapy.

＜ Recommended Grade：**B** ＞

Preoperative chemotherapy improves the rate of breast conservation.

＜ Recommended Grade：**B** ＞

Patients with pathological complete remission (pCR) reveal favorable prognosis.

U.S.

Preoperative chemotherapy should be considered for women with large clinical stage IIA, stage IIB, and T3N1M0 tumors who meet the criteria for breast-conserving therapy except for tumor size and who wish to undergo breast-conserving therapy.

＜ NCCN Categories of Consensus ：**IIA** ＞

In some patients, preoperative chemotherapy results in sufficient tumor response that breast-conserving therapy becomes possible. The results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative chemotherapy. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16:2672-2685.

＜ NCCN Categories of Consensus ：**IIA** ＞

Preoperative chemotherapy has no demonstrated disease specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumors. NSABP B-27 is a 3-arm, randomized phase III trial of women with invasive breast cancer treated with preoperative doxorubicin and cyclophosphamide (AC) chemotherapy for 4 cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by local therapy, or AC followed by local therapy followed by 4 cycles of postoperative docetaxel. Results from this study which involved 2411 women documented a higher rate of complete pathologic response at the time of local therapy in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Disease-free survival and overall survival have not been shown to be superior following docetaxel treatment in B-27. A disease-free survival advantage was observed (hazard ratio 0.71; 95% CI, 0.55 – 0.91; P=0.007) favoring preoperative versus postoperative docetaxel in the subset of patients experiencing a clinical partial response to AC.

## 26 Are adjuvant anthracycline-containing regimens beneficial for early-stage breast cancer? (☞ See CQ27)

Japan ＜ Recommended Grade：**A** ＞

Anthracycline–containing regimens are preferred as postoperative therapy.

U.S. ＜ NCCN Categories of Consensus ：**IIA** ＞

In the Early Breast Cancer Trialists' overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence (P = 0.006) and an 11% further reduction in the annual odds of death (P = 0.02) with anthracycline-containing regimens.i Based on these data, the Panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for node-positive patients. The Early Breast Cancer Trialists' analysis, however, did not consider the potential interaction between HER2 tumor status and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of those breast cancers that are HER2-positive.ii, iii,iv ,v, vi

The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive,55,56,58,59 has led to a footnote stating that anthracycline-based chemotherapy may be superior to non-anthracycline-containing regimens in the adjuvant treatment of such patients. [i] Early Breast Cancer Trialists' Collaborative Group Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet. 1998;352:930-942. [ii]Paik S, Bryant J, Tan-Chiu E, et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Natl Cancer Inst. 2000;92:1991-1998, [iii]Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst. 1998;90:1346-1360. Mass R. The role of HER-2 expression in predicting response to therapy in breast cancer. Semin Oncol. 2000;27(suppl):46-52; discussion 92-100. [iv]Menard S, Valagussa P, Pilotti S, et al. Response to cyclophosphamide, methotrexate, and fluorouracil in lymph node-positive breast cancer according to HER2 overexpression and other tumor biologic variables. J Clin Oncol. 2001;19:329-335. [v] Muss HB, Thor AD, Berry DA, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med. 1994;330:1260-1266

## 27 Is it effective to add taxane to anthracycline-based regimen as postoperative therapy for early-stage breast cancer? (☞ See CQ26)

**Japan** ＜Recommended Grade：**A**＞

It is effective to sequentially or concomitantly add taxane to anthracycline-based regimen as adjuvant therapy for lymph node -positive early-stage breast cancer.

**U.S.** ＜NCCN Categories of Consensus：**IIA**＞

The results of two randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free rates and results from one of the trials showed an improvement in overall survival with the addition of paclitaxel.i, ii [i]Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 2003;21:976-983 [ii]. Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol. 2005;23:3686-3696.

## 28 How is postoperative chemotherapy given effectively for early-stage breast cancer?

**U.S.** ＜NCCN Categories of Consensus：**IIA**＞

A number of combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized. These regimens include fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF) or cyclophosphamide, epirubicin, and fluorouracil (CEF); doxorubicin or epirubicin and cyclophosphamide (AC/EC); docetaxel, doxorubicin, and cyclophosphamide (TAC); doxorubicin or epirubicin followed by CMF; cyclophosphamide, methotrexate and fluorouracil (CMF); AC with sequential paclitaxel or docetaxel administered by a variety of schedules; doxorubicin, paclitaxel, cyclophosphamide each as a single agent for four cycles given every 2 weeks with filgrastim support (Dose-dense A – T– C); FEC followed by docetaxel; and docetaxel plus cyclophosphamide (TC). The current version of the guideline does not distinguish appropriate chemotherapy regimens by axillary lymph node status. Recent studies document substantial improvement in outcome with the incorporation of trastuzumab in the adjuvant treatment of HER2-positive breast cancer.

### 28-1 How many cycles of chemotherapy is most appropriate?

**Japan** ＜Recommended Grade：**B**＞

For anthracycline–containing regimens, 4-8 cycles are recommended varying by regimen. For CMF, 6 cycles is recommended (see p. 10-13).

**U.S.** ＜NCCN Categories of Consensus：**IIA**＞

Depending on the regimen, 3, 4, 6, or 8 cycles may be used.

### 28-2 Is it acceptable to reduce dose from the recommended standard dose since the beginning of therapy?

**Japan** ＜Recommended Grade：**B**＞

The recommended dose should not be reduced from the first dose.

**U.S.**

Not addressed

## 29 Is the dose-dense chemotherapy effective for early-stage breast cancer?

**Japan** ＜ Recommended Grade：**C** ＞

The dose-dense chemotherapy, achieving higher dose-intensity by shortening the dosing interval, may be effective in breast cancer although evidences are insufficient.

**U.S.** ＜ NCCN Categories of Consensus ：**I** ＞

Dose dense chemotherapy is an option for adjuvant therapy. A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide versus doxorubicin plus cyclophosphamide followed by paclitaxel) given either every two weeks with filgrastim support versus every three weeks. The results show no significant difference between the two chemotherapy regimens, but demonstrate a 26% reduction in hazard of recurrence (P=0.01) and a 31% reduction in the hazard of death (P=0.013) for the dose-dense regimens.

## 30 Can oral fluoropyrimidines be recommended as adjuvant therapy for early-stage breast cancer,?

**Japan** ＜ Recommended Grade：**C** ＞

Oral fluoropyrimidines are likely to be more effective than no treatment as adjuvant therapy in breast cancer patients; however, they will not be recommended since they are not considered to be the standard care.

**U.S.**

Capecitabine is not listed as an adjuvant agent.

## 31 Is the high-dose chemotherapy with hematopoietic stem cell transplantation recommended for post-operative early-stage breast cancer or metastatic/recurrent breast cancer?

**Japan** ＜ Recommended Grade：**C** ＞

The efficacy of high-dose chemotherapy as adjuvant therapy for early-stage or metastatic/recurrent breast cancer has not been clearly proven.

**U.S.**

High-dose chemotherapy with hematopoietic stem cell rescue is not recommended for breast cancer.

## 32 What first-line chemotherapy is recommended for metastatic or recurrent breast cancer?

**Japan** ＜ Recommended Grade：**A** ＞

A regimen containing anthracycline or taxane is recommended as the first-line therapy for metastatic or recurrent breast cancer.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Preferred first-line chemotherapies thus include sequential single agents or combination chemotherapy. Among preferred first-line single agents, the Panel includes doxorubicin, epirubicin, pegylated liposomal doxorubicin, paclitaxel, docetaxel, capecitabine, vinorelbine and gemcitabine. Among preferred first-line combination regimens, the Panel includes cyclophosphamide, doxorubicin, and fluorouracil (FAC/CAF); fluorouracil, epirubicin, cyclophosphamide (FEC); doxorubicin, cyclophosphamide (AC); epirubicin, cyclophosphamide (EC); doxorubicin in combination with either docetaxel or paclitaxel (AT); cyclophosphamide, methotrexate, fluorouracil (CMF); docetaxel, capecitabine; gemcitabine, paclitaxel.

## 33 What second-line chemotherapy is recommended for metastatic or recurrent breast cancer?

**Japan** ＜ Recommended Grade：**B** ＞

An anthracycline or a taxane, which has not been used in the first-line therapy, is recommended as the second-line therapy for metastatic or recurrent breast cancer.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens.

## 34 Is the third-line chemotherapy effective for metastatic or recurrent breast cancer?

**Japan** ＜ Recommended Grade：**C** ＞

Capecitabine, S-1, vinorelbine or irinotecan may be effective as the third-line chemotherapy for metastatic or recurrent breast cancer.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Failure to achieve a tumor response to 3 sequential chemotherapy regimens or an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater is an indication for supportive therapy only. In this context, failure to respond to a chemotherapy regimen means the absence of even a marginal response to the use of a given chemotherapy regimen. Response to a chemotherapy regimen followed by progression of disease is not considered a failure to experience response.

## 35 Which is a more effective chemotherapeutic regimen, concomitant administration of multiple drugs or sequential administration of single agents for metastatic or recurrent breast cancer?

**Japan** ＜ Recommended Grade：**C** ＞

Sequential single agent administration may be more effective for metastatic or recurrent breast cancer, especially in the second- or the third-line therapy.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity, and is of little survival benefit.[i]-, [ii], [iii], [iv] Thus, the Panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until progression. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression.

[i]. Carrick S, Parker S, Wilcken N, et al. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev. 2005;2:CD003372. [ii]. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 2003; 21:588-592. [iii]. O' Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin. Oncol. 2002;20:2812-2823. [iv]. Albain K, Nag S, Calderillo-Ruiz J, et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer. (MBC): First report of overall survival [meeting abstract]. J Clin Oncol. 2004;22:14s(July 15 suppl). Abstract 510.

## 36 How long should the same chemotherapy be continued when the therapy controls disease well in metastatic or recurrent breast cancer?

**Japan** ＜ Recommended Grade：**B** ＞

Continuation of anthracycline or CMF is likely to be beneficial in metastatic or recurrent breast cancer, provided that it is effective and adverse events are mild.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Limited information suggests that progression-free survival can be prolonged with the use of continuous chemotherapy versus shorter course chemotherapy.[i],[ii] Due to the lack of overall survival differences, the use of prolonged versus shorter chemotherapy needs to be weighted against the detrimental effects of continuous chemotherapy on overall quality of life.

[i]. Muss HB, Case LD, Richards F, 2nd, et al. Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. The Piedmont Oncology Association. N Engl J Med. 1991:325 1342-1348. [ii]. Falkson G, Gelman R, Pandya K, et al. Eastern Cooperative Oncology Group randomized trials of observation versus maintenance therapy for patients with metastatic breast cancer in complete remission following induction treatment. J Clin Oncol. 1998;16:1669-1676.

# Treatment by disease status

## 37 Is local intraarterial injection chemotherapy effective for locally-advanced breast cancer?

**Japan** ＜ Recommended Grade：**D** ＞

Local intraarterial injection chemotherapy should not be performed for locally-advanced breast cancer.

**U.S.**

Not addressed

## 38 What therapies are recommended for locally-advanced breast cancer (Stage IIIA (excluding T3N1MO), IIIB or IIIC)?

**Japan** ＜Recommended Grade：**B**＞

Multidisciplinary therapy including surgery and radiation after neoadjuvant chemotherapy is recommended for locally-advanced breast cancer (Stage IIIA (excluding T3N1MO), IIIB or IIIC).

**U.S.** ＜NCCN Categories of Consensus ：**IIA**＞

For patients with inoperable non-inflammatory locally advanced disease at presentation, the initial use of anthracycline-based preoperative chemotherapy with or without a taxane is standard therapy.[i] Local therapy following a clinical response to preoperative chemotherapy usually consists of (1) total mastectomy with level I/II axillary lymph node dissection, with or without delayed breast reconstruction, or (2) lumpectomy and level I/II axillary dissection. Both local treatment groups are considered to have sufficient risk of local recurrence to warrant the use of chest wall (or breast) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. In the absence of detected internal mammary node involvement, consideration may be given to including the internal mammary lymph nodes in the radiation field (category 3) . Adjuvant therapy may involve completion of planned chemotherapy regimen course if not completely preoperatively, followed by endocrine therapy in patients with hormone receptor-positive disease. . It was the consensus of the Panel that there is no role for non-endocrine-, non-trastuzumab-containing regimens following completion of the planned course of chemotherapy. [i]. Hortobagyi GN, Singletary SE, Strom EA. Locally advanced breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the Breast. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

## 39 What therapies are recommended for inflammatory breast cancer?

**Japan** ＜Recommended Grade：**B**＞

Multidisciplinary therapy including surgery and radiation after neoadjuvant chemotherapy is recommended.

**U.S.**

The treatment of patients with IBC should involve a combined modality approach.293 The benefit of preoperative chemotherapy followed by mastectomy over preoperative chemotherapy alone in patients with IBC was shown in a retrospective analysis in which lower local recurrence rates and longer disease-specific survival were reported for the combined modality approach.[i] Results from a retrospective study of patients with IBC performed over a 20-year period at M.D. Anderson demonstrated that initial treatment with doxorubicin-based chemotherapy followed by local therapy (ie, radiotherapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year disease-free survival rate of 28%.[ii] Additional support for the use of anthracycline-based preoperative chemotherapy comes from the only randomized trial of patients with IBC. In this study, 5-year survival rates of 44% were observed when epirubicin/cyclophosphamide-based regimens were administered as initial therapy.[iii] A recent retrospective study has demonstrated that addition of a taxane to an anthracycline-based regimen improved PFS and overall survival in patients with estrogen receptor-negative IBC.[iv]Inclusion of trastuzumab in the chemotherapy regimen is recommended for patients with HER2-positive disease. Patients with a clinical/pathologic diagnosis of IBC should not be treated with pre-chemotherapy surgery. Patients responding to preoperative chemotherapy should undergo mastectomy with axillary lymph node dissection; breast-conserving therapy is not recommended for patients with IBC. Any remaining planned chemotherapy should be completed postmastectomy followed sequentially by endocrine therapy in patients with hormone receptor-positive disease. If the IBC is HER2 positive, completion of one year of trastuzumab is recommended. Finally, post-mastectomy chest wall and regional node irradiation is recommended following the completion of any planned chemotherapy (see IBC-1). Mastectomy is not recommended for patients with IBC who do not respond to preoperative chemotherapy. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and patients responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above. Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease. It has been known for many years that primary surgical treatment of patients with IBC is associated with very poor outcomes.[v] Use of breast-conserving surgery in patients with IBC has been associated with poor cosmesis, and limited data suggest that rates of local recurrence may be higher when compared with mastectomy. The Panel recommends preoperative chemotherapy with an anthracycline-based regimen with or without taxanes for the initial treatment of patients with IBC (see IBC-1; BINV-14). Inclusion of trastuzumab in the chemotherapy regimen is recommended for patients with HER2-positive disease. Patients with a clinical/pathologic diagnosis of IBC should not be treated with pre-chemotherapy surgery. Patients responding to preoperative chemotherapy should undergo mastectomy with axillary lymph node dissection; breast-conserving therapy is not recommended for patients with IBC. Any remaining planned chemotherapy should be completed postmastectomy followed sequentially by endocrine therapy in patients with hormone receptor-positive disease. If the IBC is HER2 positive, completion of one year of trastuzumab is recommended. Finally, post-mastectomy chest wall and regional node irradiation is recommended following the completion of any planned chemotherapy (see IBC-1). Mastectomy is not recommended for patients with IBC who do not respond to preoperative chemotherapy. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and patients responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above. Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease [i]. Fleming RY, Asmar L, Buzdar AU, et al. Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast cancer. Ann Surg

Oncol. 1997, [ii]. Ueno NT, Buzdar AU, Singletary SE, et al. Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M.D. Anderson Cancer Center. Cancer Chemother Pharmacol. 1997;40:321-324. [iii]. Therasse P, Mauriac L, Welnicka-Jaskiewicz M, et al. Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide plus filgrastim as neoadjuvant treatment in locally advanced breast cancer: An EORTC-NCIC-SAKK Multicenter Study. J Clin Oncol. 2003;21:843-850.[iv]. Cristofanilli M, Gonzalez-Angulo AM, Buzdar AU, et al. Paclitaxel improves the prognosis in estrogen receptor negative inflammatory breast cancer: the M.D. Anderson Cancer Center experience. Clin Breast Cancer. 2004;4:415-419. [v]. Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. Breast disease. 2005,2006;22:67-73.

## 40 What therapies are recommended as postoperative drug therapy in elderly breast cancer patients?

**Japan**

< Recommended Grade : **A** >
Postoperative hormone therapy is recommended in hormone-sensitive breast cancer.

< Recommended Grade : **B** >
Chemotherapy regimens applied to younger patients are recommended only in patients with a relatively long life expectancy and who maintain good organ functions with few comorbidities.

**U.S.**

< NCCN Categories of Consensus : **IIA** >
Breast irradiation may be omitted in those 70 years old or older with estrogen-receptor positive, clinically node negative, T1 tumors who receive adjuvant endocrine therapy. Hormonal therapy is appropriate for estrogen receptor positive patients. There are insufficient data to make chemotherapy recommendations for those over 70 years old. Treatment should be individualized with consideration of comorbid conditions.

< Recommended Grade : **IIA** >
There are insufficient data to make chemotherapy recommendations for those over 70 years old. Treatment should be individualized with consideration of comorbid conditions.

## 41 What drug therapies are recommended for elderly patients with metastatic or recurrent breast cancer?

**Japan** < Recommended Grade : **B** >
Considered patient' s life expectancy and QOL, regimens applied to younger patients are recommended only in patients who maintain good organ functions with few comorbidities as younger patients.

**U.S.** < NCCN Categories of Consensus : **IIA** >
Treatment should be individualized with consideration of comorbid conditions

## 42 Has the safety of chemotherapy been established in pregnant patients with breast cancer?

**Japan**

< Recommended Grade : **D** >
Chemotherapy should not be administered during the first trimester of pregnancy.

< Recommended Grade : **C** >
The safety of chemotherapy has not been established yet in the second and third trimester of pregnancy.

**U.S.**

< Recommended Grade : **IIA** >
Chemotherapy should not be administered at any point during the first trimester of pregnancy.

< Recommended Grade : **IIA** >
Fetal malformation risks in the second and third trimester are approximately 1.3%, not different than that of fetuses not exposed to chemotherapy during pregnancy. If systemic therapy is initiated, fetal monitoring prior to each chemotherapy cycle is appropriate. Chemotherapy during pregnancy should not be given after week 35 of pregnancy or within 3 weeks of planned delivery in order to avoid the potential for hematologic complications at the time of delivery. Recent data from a single institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m2 IV day 1 and 4, doxorubicin 50 mg/m2 by IV infusion over 72 hours and cyclophosphamide 500 mg/m2 IV day 1) may be given with relative safety during the second and third trimesters of pregnancy. Johnson PH, Gwyn K, Gordon L, et al. The treatment of pregnant women with breast cancer and the outcomes of the children exposed to chemotherapy in utero [meeting abstract]. J Clin Oncol. 2005;23:16s(June 1 suppl). Abstract 540

## 43 What drug therapies are recommended for male breast cancer?

### 43-a What postoperative drug therapies are recommended in male patients with breast cancer?

**Japan**

< Recommended Grade : **B** >
Five-year treatment with tamoxifen is recommended as postoperative hormone therapy.

< Recommended Grade : **B** >
Postoperative chemotherapy in the same manner as in female patients is recommended in male patients with breast cancer.

**U.S.**

Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.

### 43-b What drug therapies are recommended for metastatic or recurrent male breast cancer?

**Japan**

< Recommended Grade : **B** >
Tamoxifen is recommended as the first-line therapy for hormone-sensitive male breast cancer.

< Recommended Grade : **B** >
It is recommended to chemotherapy in the same manner as in female patients with breast cancer for hormone-non-sensitive patients with life-threatening organ metastasis.

**U.S.**

Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.

## 44 Is drug therapy effective in brain metastasis or meningeal dissemination of breast cancer?

**Japan** < Recommended Grade : **C** >
The benefit of drug therapy in brain metastasis or meningeal dissemination of breast cancer has not been validated yet.

**U.S.**

Not addressed

## 45 Is postoperative bisphosphonate effective to prevent bone metastasis?

**Japan** < Recommended Grade : **C** >
It is not proved yet that postoperative bisphosphonate is effective to prevent bone metastasis.

**U.S.**

Not addressed

## 46 Is bisphosphonates effective for bone metastasis?

**Japan** < Recommended Grade : **A** >
Bisphosphonates decrease the incidence and delay the onset of bone metastasis-related complications, but not improve the survival for breast cancer patients with bone-metastasis.

**U.S.** < NCCN Categories of Consensus : **I** >
The use of bisphosphonates in metastatic disease is a palliative care measure. No impact on overall survival has been observed in patients treated with bisphosphonates. Bisphosphonate treatment is of value in patients with metastatic breast cancer in bone.204,[i] Women with bone metastasis, especially if lytic, should be given a bisphosphonate (eg, pamidronate or zoledronic acid) in combination with calcium citrate and vitamin D if expected survival is 3 months or longer and creatinine levels are below 3.0 mg/dL (category 1).204,[ii]-, [iii], [iv], [v], [vi], [vii] Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.[viii],[ix] There are extensive data from randomized trials in support of the use of bisphosphonates for patients with metastatic disease to bone. The randomized clinical trial data includes the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.210,211,216-,[x],[xi],[xii],[xiii],[xiv] In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events, pathologic fractures, and less need for radiation therapy and surgery to treat bone pain. There are extensive data from randomized trials in support of the use of bisphosphonates for patients with metastatic disease to bone. The randomized clinical trial data includes the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.210,211,216-,[x],[xi],[xii],[xiii],[xiv] In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events, pathologic fractures, and less need for radiation therapy and surgery to treat bone pain.[i]. Theriault RL, Biermann JS, Brown E, et al. NCCN Task Force Report: Bone Health and Cancer Care. J Natl Compr Canc Netw. 2006; 4 Suppl 2: S1-S20.[ii]. Conte PF, Latreille J, Mauriac L, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous

pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. J Clin Oncol. 1996;14:2552-2559. [iii]. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol. 1998;16:2038-2044.[iv]. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol. 1999;17:846-854.[v]. Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer. 2001;91:1191-1200.[vi]. Ali SM, Esteva FJ, Hortobagyi G, et al. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. J Clin Oncol. 2001;19:3434-3437.[vii]. Theriault RL. The role of bisphosphonates in breast cancer. J Natl Compr Canc Netw. 2003;1:232-241. [viii]. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J. 2001;7:377-387. [ix]. Rosen LS, Gordon DH, Dugan Jr. W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer. 2004;100:36-43. [x]. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer. 2000; 88:1082-1090. [xi]. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med. 1996; 335:1785-1971. [xii]. Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer. 2004;40:1704-1712. [xiii]. McLachlan SA, Cameron D, Murray R, et al. Safety of oral ibandronate in the treatment of bone metastases from breast cancer: long-term follow-up experience. Clin Drug Investig. 2006;26:43-48. [xiv]. Pecherstorfer M, Rivkin S, Body JJ, et al. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. Clin Drug Investig. 2006; 26:315-322.

### 47 Is it effective to use non-opioid or opioid analgesic agents for pain control in patients with bone metastasis of breast cancer?

**Japan** ＜ Recommended Grade：**A** ＞

Analgesic therapy should be performed according to the 3-grade analgesic ladder proposed by the WHO in the case of cancer pain.

**U.S.** ＜ NCCN Categories of Consensus ：**IIA** ＞

Not addressed by the NCCN Breast Cancer Guideline; however, the Cancer Pain Guideline does recommend both opioid and nonopioid agents for pain control.

### 48 Is intraarterial injection chemotherapy effective for liver metastasis from breast cancer?

**Japan** ＜ Recommended Grade：**D** ＞

Intraarterial injection chemotherapy should not be performed for liver metastasis from breast cancer.

**U.S.**

Not addressed.

### 49 Is an opioid analgesic agent effective to control respiratory symptoms in patients with lung metastasis from breast cancer who presents with dyspnea?

**Japan** ＜ Recommended Grade：**B** ＞

Morphine can be safely administered for dyspnea and cough to improve patient' s QOL with caution to respiratory depression.

**U.S.**

Not addressed.

## Countermeasures against adverse events

### 50 Are 5-HT3 receptor-antagonistic antiemetics or steroids effective for chemotherapy-induced nausea/vomiting?

**Japan**

＜ Recommended Grade：**A** ＞

Concommitant use of 5-HT3 receptor-antagonistic antiemetics and steroid is effective for acute emesis/vomiting.

＜ Recommended Grade：**B** ＞

In the case of delayed emesis/vomiting, steroid or 5-HT3 receptor-antagonistic antiemetics is recommended based on emetogenicity of chemotherapeutic agents.

**U.S.**

NCCN Antiemesis Guideline.

## 51 Is granulocyte-colony stimulating factor (G-CSF) or oral antibiotics effective in chemotherapy-induced neutropenia to prevent or treat febrile neutropenia?

**Japan** ＜ Recommended Grade：**C** ＞

The effectiveness of G-CSF has not been proven for non-febrile neutropenia.

**U.S.**

See NCCN Myeloid Growth Factors Guideline and Cancer-Related Infections Guideline

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**Japan** ＜ Recommended Grade：**B** ＞

In the case of febrile neutropenia, it is considered to use G-CSF in addition to antibiotics.

**U.S.**

See NCCN Myeloid Growth Factors Guideline and Cancer Treatment \-Related Infections Guideline

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**Japan** ＜ Recommended Grade：**B** ＞

In the case of low-risk febrile neutropenia with relatively favorable systemic conditions, it is recommended to use oral antibiotics rather than intravenous antibiotics.

**U.S.**

See NCCN Cancer Treatment-Related Infections Guideline

## 52 Is there any effective measures for alopecia caused by chemotherapy?

**Japan** ＜ Recommended Grade：**C** ＞

There are no effective established measures for alopecia caused by chemotherapy.

**U.S.**

Not addressed

## 53 What treatments are recommended to prevent or treat numbness or edema caused by taxanes?

**Japan**

＜ Recommended Grade：**C** ＞

There is no established effective treatment to prevent or treat peripheral nerve disorders such as numbness caused by taxanes.

＜ Recommended Grade：**B** ＞

Administration of a corticosteroid is effective to prevent edema caused by docetaxel.

**U.S.**

Not addressed

## 54 Is it possible to become pregnant after chemotherapy or during/after hormone therapy?

**U.S.**

Some women appear to become postmenopausal on tamoxifen therapy, have resumption of ovarian function after discontinuation of tamoxifen.

### 54-1 Is it possible to become pregnant after chemotherapy or hormone therapy?

**Japan** ＜ Recommended Grade：**B** ＞

It is possible to become pregnant and have normal delivery if the normal ovarian functions are maintained. The incidence of perinatal abnormalities or fetal deformities does not increase in pregnancy/delivery after chemotherapy or hormone therapy.

**U.S.**

Not addressed; however, many of the agents used in cancer-directed therapy contain warnings against becoming pregnant while on these agents.

### 54-2 Is it possible to conceive during hormone therapy?

**Japan** ＜ Recommended Grade：**D** ＞

Pregnancy during hormone therapy is not recommended due to teratogenicity of tamoxifen.

**U.S.**

Not addressed; however, many of the agents used in cancer-directed therapy contain warnings against becoming pregnant while on these agents.

## 55 Is the incidence of chemotherapy-induced menopause decreased by using an LH-RH analogue in combination with chemotherapy in premenopausal hormone-insensitive early-stage breast cancer?

**Japan** ＜Recommended Grade：**C**＞

Concomitant use of LH-RH analogue during chemotherapy would decrease the incidence of chemotherapy-induced menopause. However, it is not recommended at present due to lack of evidences for its safety.

**U.S.**

Not addressed

## 56 What measures are recommended for hot flush caused by hormone therapy?

**Japan** ＜Recommended Grade：**B**＞

Paroxetine or alteration of hormonal agents is recommended if a patient develops significant hot flush from hormone therapy.

**U.S.**

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine has specifically been studied and is an effective intervention in decreasing hot flashes.[i] Recent evidence has suggested that concomitant use of tamoxifen with certain selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine and fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.[ii],[iii] These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, the SSRIs citalopram and venlafaxine appear to have only minimal effects on tamoxifen metabolism. Premenopausal women who experience early ovarian failure secondary to adjuvant chemotherapy and postmenopausal women who are treated with an aromatase inhibitor are at increased risk for the development of osteopenia or osteoporosis with an associated increased risk of bone fracture. The guideline thus recommends monitoring of bone health during surveillance in these high risk women[iv] [i]. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet. 2000;356:2059-2063. [ii]. Garber K. Tamoxifen pharmacogenetics moves closer to reality. J Natl Cancer Inst. 2005;97:412-413. [iii]. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst. 2005;97:30-39. [iv]. Hillner BE, Ingle JN, Chlebowski RT, et al.. American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol. 2003;21:4042-4057.

## 57 What measures are effective to prevent or treat osteoporosis for patients on aromatase inhibitor?

**Japan** ＜Recommended Grade：**B**＞

For patients on aromatase inhibitor who have osteoporosis or high risk of osteoporosis, bisphosphonates and annual bone mineral densitometry are recommended.

**U.S.**

Postmenopausal women who are treated with an aromatase inhibitor are at increased risk for the development of osteopenia or osteoporosis with an associated increased risk of bone fracture. The guideline thus recommends monitoring of bone health during surveillance in these high risk women. Hillner BE, Ingle JN, Chlebowski RT, et al.. American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol. 2003;21:4042-405

## 58 What are adverse events from bisphosphonates? What treatments are recommended?

**Japan** ＜Recommended Grade：**B**＞

Hypocalcemia, renal dysfunction and osteonecrosis of the jaw are remarkable adverse events from bisphosphonates. It is recommended to examine whether patients have any risk factors of renal dysfunction or dental diseases before administration of bisphosphonates, and when an adverse event has occurred, it is necessary to discontinue bisphosphonates and treat the event accordingly.

**U.S.** ＜NCCN Categories of Consensus：**IIA**＞

The risk of renal toxicity necessitates monitoring of serum creatinine prior to administration of each dose and dose reduction or discontinuation if renal function is reduced. Osteonecrosis of the jaw, a recently reported complication of bisphosphonate treatment, has been described. In a review of more than 16,000 cancer patients, an increased risk of jaw or facial bone surgery along with an increased risk of being diagnosed with inflammatory conditions or osteomyelitis of the jaw with the use of intravenous bisphosphonates was documented. An absolute risk of 5.48 events per 100 patients treated was seen, with an increase in risk associated with an increase in cumulative

dose of drug.[i] A dental examination with preventive dentistry intervention is recommended prior to treatment with intravenous bisphosphonates and dental procedures during treatment with intravenous bisphosphonates should be avoided if at all possible. Additional risk factors for the development of osteonecrosis of the jaw include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.[ii] Confirmation of metastatic disease by imaging including x-ray, CT or MRI; and initial evaluation of serum calcium, creatinine, phosphorous and magnesium levels should be undertaken prior to the initiation of intravenous bisphosphonate treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous and magnesium may be prudent since hypophosphotemia and hypocalcemia have been reported. [i]. Wilkinson GS, Kuo YF, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. J Natl Cancer Inst. 2007;99: 1016-1024. [ii]. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Systematic Review Bisphosphonates Osteonecrosis of the Jaw. Ann Intern Med. 2006;144:753-761.

## Breast cancer-preventing drugs

### 59 What drugs are useful to prevent onset of breast cancer? What chemoprevention is proven to be effective for breast cancer?

**Japan** ＜ Recommended Grade：**C** ＞

Chemoprevention by tamoxifen or raloxifen is effective for high-risk women of breast cancer. However, a serious adverse event may occur and risk factors of developing breast cancer among Japanese women have not been clarified yet. Therefore chemoprevention should not be implemented in daily clinical practice.

**U.S.**

See NCCN Breast Cancer Risk Reduction Guideline

### 60 Is vaccination for influenza recommended to patients during chemotherapy?

**Japan** ＜ Recommended Grade：**B** ＞

Inactivated influenza vaccine is preffered to being administered before or during chemotherapy.

**U.S.**

See NCCN Cancer Treatment-Related Infection Guideline

## Alternative medicine

### 61 Is any complementary and alternative medicine effective as a treatment of breast cancer?

**Japan**

＜ Recommended Grade：**D** ＞

There are no complementary and alternative medicines to suppress progression of breast cancer or improve the survival and those should not be administered.

＜ Recommended Grade：**C** ＞

Some complementary and alternative medicines are effective for palliation of cancer pain or adverse events due to standard cancer therapy, or alleviation of anxiety.

**U.S.**

Not addressed.