Breast Cancer (Invasive; Nonmetastatic) Treatment Regimens

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The National Comprehensive Cancer Network Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Note: All recommendations are category 2A unless otherwise indicated.

▶Adjuvant Endocrine Therapy[1]

REGIMEN	DOSING
Hormone Receptor-Positive Disease	
Premenopausal at diagnosis	
Tamoxifen (with or without Leuprolide or Goserelin) followed by Aromatase Inhibitor[2-15]	Tamoxifen[a] 20mg orally once daily for 5 years (Category 1) **with or without** **Day 1:** Leuprolide[b] 3.75mg IM of 28-day cycle (Category 1) **OR** **Day 1:** Goserelin[b] 3.6mg subcutaneous of 28-day cycle (Category 1) **followed by** (for post-menopausal women) Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily for 5 years (Category 1).
Tamoxifen (with or without Leuprolide or Goserelin)[2,6-14,16]	Tamoxifen[a] 20mg orally once daily for 5 years (Category 1), **with or without** **Day 1:** Leuprolide[b] 3.75mg IM of 28-day cycle (Category 1) **OR** **Day 1:** Goserelin[b] 3.6mg subcutaneous of 28-day cycle (Category 1)
Tamoxifen (with or without Leuprolide or Goserelin) followed by consideration of Tamoxifen[2,6-14,16]	Tamoxifen[a] 20mg orally once daily for 5 years (Category 1) **with or without** **Day 1:** Leuprolide[b] 3.75mg IM of 28-day cycle (Category 1) **OR** **Day 1:** Goserelin[b] 3.6mg subcutaneous of 28-day cycle (Category 1) **followed by** (for pre- or postmenopausal women) Tamoxifen[a] 20mg orally once daily for an additional 5 years.
Aromatase inhibitor (with Leuprolide or Goserelin)[3-14,17,18]	Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily for 5 years (Category 1) **AND** **Day 1:** Leuprolide[b] 3.75mg IM of 28-day cycle(Category 1) **OR** **Day 1:** Goserelin[b] 3.6mg SC of 28-day cycle (Category 1).
Postmenopausal at diagnosis	
Aromatase inhibitor followed by consideration of an Aromatase Inhibitor[3-5,18-23]	Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily for 5 years (Category 1) **followed by** Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily for an additional 5 years.
Aromatase inhibitor followed by Tamoxifen[2-4, 25]	Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily for 2 to 3 years (Category 1) **followed by** Tamoxifen[a] 20mg orally once daily to complete 5 years of endocrine therapy (Category 1).
Tamoxifen followed by an Aromatase Inhibitor[2-5,26-42]	Tamoxifen[a] 20mg orally once daily for 2 to 3 years **followed by** Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily to complete 5 years of endocrine therapy (Category 1).
	Tamoxifen[a] 20mg orally once daily for 2 to 3 years **followed by** Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily for up to 5 years of an aromatase inhibitor (Category 2B).
	Tamoxifen[a] 20mg orally once daily for 4 to 6.5 years **followed by** Anastrozole[c] 1mg orally once daily **OR** Exemestane[c] 25mg orally once daily **OR** Letrozole[c] 2.5mg orally once daily for 5 years (Category 1).

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Breast Cancer (Invasive; Nonmetastatic) Treatment Regimens

▶Adjuvant Endocrine Therapy[1] (continued)

REGIMEN	DOSING
Hormone Receptor-Positive Disease (continued)	
Postmenopausal at diagnosis (continued)	
Tamoxifen followed by consideration of Tamoxifen[2,8,16]	Tamoxifen[a] 20mg orally once daily for 4 to 6.5 years **followed by** Tamoxifen[a] 20mg orally once daily to complete 10 years of endocrine therapy.
Postmenopausal patients with contraindication to aromatase inhibitors or who cannot tolerate or decline aromatase inhibitor	
Tamoxifen[2,8,16]	Tamoxifen[a] 20mg orally once daily for 5 years (Category 1).
	Tamoxifen[a] 20mg orally once daily for up to 10 years.

▶Neoadjuvant/Adjuvant Chemotherapy[1,d-j]

HER2-negative Disease	
Preferred Regimens	
Dose-dense AC followed by paclitaxel (Category 1)[43,k,l]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 14 days for 4 cycles (all cycles are with myeloid growth factor support; refer to NCCN Guidelines for Myeloid Growth Factors), **followed by** **Day 1:** Paclitaxel 175mg/m^2 via 3-hour IV infusion. Repeat cycle every 14 days for 4 cycles. All cycles are with myeloid growth factor support.
Dose-dense AC followed by weekly paclitaxel (Category 1)[43,k,i]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 14 days for 4 cycles, **followed by** **Day 1:** Paclitaxel 80mg/m^2 via 1-hour IV infusion weekly for 12 weeks. All cycles are with myeloid growth factor support.
TC (Category 1)[44,l]	**Day 1:** Docetaxel 75mg/m^2 IV over 60 minutes **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 4 cycles. All cycles are with myeloid growth factor support.
Capecitabine (if triple-negative breast cancer and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy. Category 1)[45]	**Days 1-14:** Capecitabine 1000-1250mg/m^2 orally twice daily every 21 days for 6-8 cycles.
Useful in Certain Circumstances	
Dose-dense AC (Category 1)[43,l]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV. Repeat cycle every 14 days for 4 cycles. All cycles are with myeloid growth factor support.
AC followed by weekly paclitaxel (Category 1)[46]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 4 cycles, **followed by** **Day 1:** Paclitaxel 80mg/m^2 by 1-hour IV infusion weekly for 12 weeks.
CMF (Category 1)[47]	**Days 1–14:** Cyclophosphamide 100mg/m^2 orally **Days 1 and 8:** Methotrexate 40mg/m^2 IV push **Days 1 and 8:** Fluorouracil 600mg/m^2 IV push. Repeat cycle every 28 days for 6 cycles.
AC (Category 2B)[48]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 4 cycles.

continued

Breast Cancer (Invasive; Nonmetastatic) Treatment Regimens

▶Neoadjuvant/Adjuvant Chemotherapy[1,d-j] (continued)

REGIMEN	DOSING
HER2-negative Disease (continued)	
Other Recommended Regimens	
AC followed by docetaxel (Category 1)[49]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 4 cycles, **followed by** **Day 1:** Docetaxel 100mg/m^2 IV over 60 minutes. Repeat cycle every 21 days for 4 cycles.
EC (Category 1)[50]	**Day 1:** Epirubicin 100mg/m^2 IV push **Day 1:** Cyclophosphamide 830mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 8 cycles.
TAC (Category 1)[51,l]	**Day 1:** Docetaxel 75mg/m^2 IV over 60 minutes **Day 1:** Doxorubicin 50mg/m^2 IV push **Day 1:** Cyclophosphamide 500mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 6 cycles. All cycles are with myeloid growth factor support.
HER2-positive Disease[m]	
Preferred Regimens[n,o]	
AC followed by paclitaxel + trastuzumab[58,59,p,q]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 4 cycles, **followed by** **Day 1:** Paclitaxel 80mg/m^2 via 1-hour IV infusion weekly for 12 weeks, **with** **Day 1:** Trastuzumab 4mg/kg IV over 90 minutes with first dose of paclitaxel, then 2mg/kg IV over 30 minutes weekly to complete 1 year of trastuzumab therapy. As an alternative, trastuzumab 6mg/kg IV over 30 minutes every 21 days may be used following the completion of paclitaxel, and given to complete 1 year of trastuzumab treatment.
AC followed by paclitaxel + trastuzumab + pertuzumab[58-60,p,q]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Repeat cycle every 21 days for 4 cycles, **followed by** **Day 1:** Pertuzumab 840mg IV over 60 minutes for cycle 1, then 420mg IV over 30 minutes for cycles 2-4 **Day 1:** Trastuzumab 8mg/kg IV over 90 minutes for cycle 1, then 6mg/kg IV over 30 minutes for cycles 2-4 **Days 1, 8, and 15:** Paclitaxel 80mg/m^2 IV over 60 minutes. Repeat cycle every 21 days for 4 cycles, **followed by** **Day 1:** Trastuzumab 6mg/kg IV over 30 minutes **Day 1:** Pertuzumab 420 mg IV over 30 minutes. Repeat cycle every 21 days to complete 1 year of trastuzumab and pertuzumab therapy.
Dose-dense AC followed by paclitaxel + trastuzumab[58,61,l,p,q]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes Repeat cycle every 14 days for 4 cycles, **followed by** **Day 1:** Paclitaxel 175mg/m^2 via 3-hour IV infusion. Cycled every 14 days for 4 cycles, **with** **Day 1:** Trastuzumab 4mg/kg IV over 90 minutes with first dose of paclitaxel, then 2mg/kg IV over 30 minutes weekly to complete 1 year of trastuzumab therapy. As an alternative, trastuzumab 6mg/kg IV over 30 minutes every 21 days may be used following the completion of paclitaxel, and given to complete 1 year of trastuzumab treatment. All cycles are with myeloid growth factor support.
Paclitaxel + trastuzumab[58,62,r]	**Day 1:** Paclitaxel 80mg/m^2 IV over 60 minutes weekly for 12 weeks **with** **Day 1:** Trastuzumab 4mg/kg IV over 90 minutes with first dose of paclitaxel, then 2 mg/kg IV over 30 minutes weekly to complete 1 year of trastuzumab therapy **OR** **Day 1:** Trastuzumab 6mg/kg IV over 30 minutes every 21 days to complete 1 year of trastuzumab therapy following the completion of paclitaxel.

continued

Breast Cancer (Invasive; Nonmetastatic) Treatment Regimens

▶Neoadjuvant/Adjuvant Chemotherapy[1,d-i] (continued)

REGIMEN	DOSING
HER2-positive Disease (continued)	
Preferred Regimens[n,o] (continued)	
TCH[58,63,l,q]	**Day 1:** Trastuzumab 4mg/kg IV over 90 minutes for cycle 1, then 2mg/kg IV over 30 minutes weekly to complete 18 cycles, **with** **Day 1:** Docetaxel 75mg/m^2 IV over 60 minutes, **with** **Day 1:** Carboplatin AUC 6 IV over 30 minutes cycled every 21 days for 6 cycles, **followed by** **Day 1:** Trastuzumab 6mg/kg IV over 30 minutes every 21 days to complete 1 year of trastuzumab therapy. As an alternative, trastuzumab 8mg/m^2 IV over 90 minutes may be used on day 1 of cycle 1, then 6mg/kg IV over 30 minutes to complete 1 year of trastuzumab therapy. All cycles are wtih myeloid growth factor support.
TCH + pertuzumab[58,60,64,l,q]	**Day 1:** Trastuzumab 8mg/kg IV over 90 minutes for cycle 1, then 6mg/kg IV over 30 minutes every 21 days for cycles 2-6 **Day 1:** Pertuzumab 840mg IV over 60 minutes for cycle 1, then 420 mg IV over 30 minutes every 21 days for cycles 2-6 **Day 1:** Docetaxel 75mg/m^2 IV over 60 minutes **Day 1:** Carboplatin AUC 6 IV over 30 minutes. Repeat cycle every 21 days for cycles 1-6, **followed by** **Day 1:** Trastuzumab 6mg/kg IV over 30 minutes every 21 days to complete 1 year of trastuzumab therapy **Day 1:** Pertuzumab 420mg IV over 30 minutes to complete 1 year of pertuzumab therapy. All cycles are with myeloid growth factor support.
Useful in Certain Circumstances	
Docetaxel + cyclophosphamide + trastuzumab[58,65,q,r]	**Day 1:** Docetaxel 75mg/m^2 IV over 60 minutes **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Cycled every 21 days for 4 cycles, **with** **Day 1:** Trastuzumab 4mg/kg IV over 90 minutes week 1, then 2mg/kg IV over 30 minutes weekly for 11 weeks, then 6mg/kg every 21 days to complete 1 year of trastuzumab therapy **OR** **Day 1:** Trastuzumab 8mg/kg IV over 90 minutes cycle 1, then 6mg/kg IV over 30 minutes every 21 days to complete 1 year of trastuzumab therapy.
Other Recommended Regimens	
AC followed by docetaxel + trastuzumab[58,62,66,p,q]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV over 30 minutes. Cycled every 21 days for 4 cycles, **followed by** **Day 1:** Docetaxel 100mg/m^2 IV over 60 minutes. Cycled every 21 days for 4 cycles, **with** **Day 1:** Trastuzumab 4mg/kg IV over 90 minutes week 1, then 2mg/kg IV over 30 minutes weekly for weeks 2-12, then 6mg/kg IV over 30 minutes every 21 days to complete 1 year of trastuzumab therapy.
AC followed by docetaxel + trastuzumab + pertuzumab[58,60,67,p,q]	**Day 1:** Doxorubicin 60mg/m^2 IV push **Day 1:** Cyclophosphamide 600mg/m^2 IV 0ver 30 minutes. Repeat cycle every 21 days for 4 cycles, **followed by** **Day 1:** Pertuzumab 840mg IV over 60 minutes for cycle 1, then 420mg IV over 30 minutes for cycles 2-4 **Day 1:** Trastuzumab 8mg/kg IV over 90 minutes for cycle 1, then 6mg/kg IV over 30 minutes for cycles 2-4 **followed by** **Day 1:** Docetaxel 75mg/m^2 IV over 60 minutes for cycle 1, then 100mg/m^2 IV over 60 minutes for cycles 2-4 (if tolerated). Repeat cycle every 21 days for 4 cycles, **followed by** **Day 1:** Trastuzumab 6mg/kg IV over 30 minutes and Pertuzumab 420 mg IV over 30 minutes every 21 days to complete 1 year of trastuzumab and pertuzumab therapy.

[a] Some SSRIs like fluoxetine and paroxetine decrease the formation of impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against *CYP2D6* gene testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of *CYP2D6* should be used with caution.

[b] A balanced discussion of the risk and benefits associated with ovarian suppression therapy is critical. Aromatase inhibitor or tamoxifen for 5 years plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal women at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement).

[c] The three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

[d] The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a healthcare delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

[e] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to nonanthracycline-based regimens in patients with HER2-positive tumors.

[f] Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

[g] CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.

continued

[h] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.

[i] Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125mg/m^2.

[j] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving neoadjuvant/adjuvant chemotherapy. Results may be less effective with anthracycline-containing regimens.

[k] It would be acceptable to change the administration sequence to paclitaxel followed by dose-dense AC.

[l] All cycles are with myeloid growth factor.

[m] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab.[52,53] It has different dosing and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine. (Trastuzumab and hyaluronidase-oysk 600mg subcutaneous over 2-5 minutes. Cycle length is regimen specific. Trastuzumab and hyalruonidase-oysk is administered as a substitute for intravenous trastuzumab on the days that intravenous trastuzumab is administered as per the regimen. This agent dose not require a loading dose. No dose adjustments for patient body weight or for different concomitant chemotherapy are required). An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[n] If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab (Category 1) +/- pertuzumab. Consider extended neratinib (Neratinib 240mg orally once daily for 1 year following adjuvant trastuzumab-containing therapy for patients with hormone receptor-positive, HER2-positive disease with a perceived high risk of recurrence).[54,55] The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.

[o] If residual disease after preoperative therapy: Ado-trastuzumab emtansine alone (Category 1; Ado-trastuzumab emtansine 3.6mg/kg IV every 21 days for 14 cycles. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (Category 1) +/- pertuzumab to complete one year of therapy.[56,57] Consider extended neratinib (Neratinib 240mg orally once daily for 1 year following adjuvant trastuzumab-containing therapy for patients with hormone receptor-positive, HER2-positive disease with a perceived high risk of recurrence).[54,55] The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.

[p] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[q] Evaluate left ventricular ejection fraction (LVEF) before and during treatment. Although the optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known, the FDA label recommends LVEF measurements every 3 months during treatment.

[r] Paclitaxel + trastuzumab may be considered for patients with low-risk, T1, N0, M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

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