Invasive Breast Cancer

PREOPERATIVE/ADJUVANT THERAPY REGIMENS [a,b,c,d,e,f]

HER2-Negative [g]

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[h]
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[h]
- TC (docetaxel and cyclophosphamide)
- If triple-negative breast cancer and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline- based chemotherapy: capecitabine[i]

Useful in certain circumstances:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by weekly paclitaxel

Other recommended regimens:

- AC followed by docetaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide

[a] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-postiive tumors.

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

[c] 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.

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

[e] 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.

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

[g] The regimens listed for HER-2 negative are all category 1 (except where indicated) when used in the adjuvant setting.

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

[i] Capecitabine 1,000 – 1250 mg/m^2 PO twice daily on days 1 -14. Cycled every 21 days for 6 – 8 cycles. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376:2147-2159.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical, trial. Participation in clinical trials is especially encouraged.

Invasive Breast Cancer
PREOPERATIVE/ADJUVANT THERAPY REGIMENS [a,b,c,d,e,f]

HER2-Positive [j]

Preferred regimens:
- AC followed by T + trastuzumab[k]
- (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- AC followed by T + trastuzumab + pertuzumab[k] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab)
- Paclitaxdel + trastuzumab
- TCH (docetaxel/carboplatin/ trastuzumab)
- TCH (docetaxel/carboplatin/ trastuzumab) + pertuzumab
- 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.[M]
- If residual disease after preoperative therapy: Ado- trastuzumab emtansine (category 1) alone n If ado- trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[M]

Useful in certain circumstances:
- Docetaxel + cyclophosphamide + trastuzumab[l]

Other recommended regimens:
- AC followed by docetaxel + trastuzumab[k] (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab)
- AC followed by docetaxel + trastuzumab + pertuzumab[k]
- (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab plus pertuzumab)

[a] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-postiive tumors.

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

[c] 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.

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

[e] Albumin-bound 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.

[f] **Consider scalp cooling to reduce the incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.**

[j] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado- trastuzumab emtansine.

[k] 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.

[i] 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.

[m] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk or recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.

[n] Ado-trastuzumab emtansine 3.6mg/kg cycled every 21 days for 14 cycles. Von Minckwitz G, Huang C, Mano M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019 ; 380 :617-628.

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Invasive Breast Cancer
CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b]

HER2-Negative

Preferred regimens:
- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- PARP inhibitors (options for patients with HER2-negative tumors and germline BRCA1/2 mutation)[d]
  - Olaparib[d] (category 1)
  - Talazoparib[d] (category 1)
- Platinum (option for patients with triple-negative tumors and germline BRCA ½ mutation)[d]
  - Carboplatin
  - Cisplatin
- Atezolizumab + albumin-bound paclitaxel (option for patients with PD-L1-positive TNBC)[e]

Other recommended regimens[c]:
- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone

Useful in certain circumstances[c]:
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/docetaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[f]

HER2-Positive[g]

Preferred regimens:
- Pertuzumab + trastuzumab + docetaxel (category 1)[h]
- Pertuzumab + trastuzumab + paclitaxel[g]

Other recommended regimens[i]:
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel[h]
- Trastuzumab + vinorelbine[h]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[h,i,j]

a Albumin-bound 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.

b **Consider scalp cooling to reduce the incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.**

c Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

d Patients with HER2-negative disease, strongly consider for germline BRCA 1/2 testing.

e Patients with TNBC, assess PD-L1 biomaker status on tumor-infiltrating immune cells to identify patients most likely to benefit from atezolizumab plus albumin-bound paclitaxel.

f Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

g Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastumuzab emtansine.

h Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

i 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.

j Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

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