

Systemic Therapy for Early Breast Cancer - Quick Reference Guide -

Effective Date: April 2021



Recommendations

Chemotherapy for Non-Metastatic Breast Cancer

1. The decision for adjuvant/neoadjuvant chemotherapy should be guided by the subtype of breast cancer (hormone receptor [HR]-positive/human epidermal growth factor receptor 2 [HER2]-negative, HER2-positive, and triple negative (TN)), prognosis, benefits (absolute gains in disease free survival [DFS] and overall survival [OS]), toxicity risks, overall health of patient, and preference of patient.^{1, 2} (*Level of Evidence: I, Strength of Recommendation: A*)
2. Individualized prognosis and expected benefit from systemic treatments, including chemotherapy, can be estimated using an online calculator such as NHS Predict which considers: patient age and menopausal status, presentation (screen detected versus symptomatic), tumour size, axillary lymph node status, and the status of estrogen receptor (ER), HER2 and Ki67 if known.³ In some patients with ER-positive/HER2-negative early breast cancer, prognosis +/- benefit of chemotherapy can be estimated from gene expression profile (GEP) testing.^{4, 5} Figure 1 outlines OncotypeDX testing eligibility in Alberta.
3. Figure 2 outlines an approach to chemotherapy decision-making for HR-positive/HER2-negative breast cancer, Figure 3 for HER2-positive, and Figure 4 for TN.^{1, 2, 6-9} (*Level of Evidence: I, Strength of Recommendation: A*)
4. As for the decision to use chemotherapy, the choice of regimen should also be guided by prognosis, benefits (absolute gains in DFS and OS where applicable), toxicity risks, overall health of patient, and preference of patient. In addition to the listed adjuvant chemotherapy regimens, other evidence-based options exist, and may be used based on clinical discretion and in review with multidisciplinary breast cancer tumour board.
5. Delays in initiating adjuvant chemotherapy should be avoided.¹⁰ Adjuvant chemotherapy should be started, as soon as surgical healing has been completed and ideally not later than 12 weeks following surgery.¹ (*Level of Evidence: I, Strength of Recommendation: A*)
6. In patients with known cardiac dysfunction or significant cardiac risk, a non-anthracycline adjuvant chemotherapy regimen is preferred. (*Level of Evidence: I, Strength of Recommendation: A*) If trastuzumab is required, consider upfront referral to cardiology.¹¹⁻¹³ (*Level of Evidence: V, Strength of Recommendation: A*)
7. Offer young women referral to a fertility clinic prior to initiation of adjuvant systemic therapies if future pregnancies are potentially desired.¹⁴ (*Level of Evidence: V, Strength of Recommendation: A*) In addition to standard fertility preservation methods or if standard fertility preservation methods are not feasible, use of a luteinizing hormone-releasing hormone (LHRH) agonist during chemotherapy can be discussed with the goal of reducing the likelihood of chemotherapy-induced ovarian insufficiency.^{14, 15} (*Level of Evidence: II, Strength of Recommendation: B*)
8. Use primary granulocyte colony-stimulating factor (GCSF) prophylaxis with dose dense regimens and regimens in which the risk of febrile neutropenia is greater than or equal to 20%.¹⁶ Use secondary GCSF prophylaxis if there was a neutropenic complication in previous chemotherapy

cycle and if dose-reduction is expected to compromise oncologic outcomes.¹⁶ (*Level of Evidence: I, Strength of Recommendation: A*)

Chemotherapy for Hormone Receptor-Positive/HER2-Negative Breast Cancer

1. Decision-making about chemotherapy in this group is complex as there is a wide range for prognosis, stage for stage, driven by underlying tumour biology. The American Joint Committee on Cancer (AJCC) 8th Edition incorporates prognostic stage grouping for hormone receptor-positive breast cancer that not only considers T-stage and N-stage, but also grade, ER-status, progesterone receptor (PR)-status, and the OncotypeDX Recurrence Score (RS) (if less than 11) when available.¹⁷
2. Favourable tumour biology is suggested by a luminal A molecular signature or luminal A-like characteristics (high ER & PR expression AND grade 1-2 and/or low Ki67 score).^{1, 2}
3. Less favourable tumour biology is suggested by a luminal B molecular signature or luminal B-like characteristics (high or low ER expression AND low PR expression or PR-negative AND grade 2-3 and/or higher Ki67 score).^{1, 2}
4. The predicted absolute overall survival benefit of chemotherapy is low for most patients with favourable tumour biology. However, the predicted absolute overall survival benefit of chemotherapy can be quite variable for patients with less favourable tumour biology. NHS Predict, and in eligible patients, OncotypeDX testing, can aid with prognostication and chemotherapy decision-making.^{5, 18} (*Level of Evidence: I, Strength of Recommendation: A*)

Hormonal Therapy

1. Adjuvant hormonal therapy should be discussed with all patients who have undergone resection of HR+ early breast cancer.^{1, 2, 19, 20} (*Level of Evidence: I, Strength of Recommendation: A*)
2. The decision to proceed with adjuvant hormonal therapy should be guided by prognosis, benefits (absolute gains in DFS and OS where applicable), toxicity risks, overall health of patient, and preference of patient.^{1, 2, 19, 20} (*Level of Evidence: I, Strength of Recommendation: A*)
3. Figure 5 outlines an approach to hormonal therapy decision-making for HR-positive/HER2-negative breast cancer.^{1, 2, 19, 20} (*Level of Evidence: I, Strength of Recommendation: A*)
4. The choice of adjuvant hormonal therapy regimen and duration of therapy should be guided by menopausal status, prognosis, benefits (absolute gains in DFS and OS), toxicity risks, overall health of patient, and preference of patient. Extending AI therapy beyond 5 years is associated with a small DFS benefit only and has not been shown to improve OS.²⁰
5. Menopausal status:²¹ Patients are clearly premenopausal if they demonstrate regular menses without using oral contraception or hormone replacement therapy prior to breast cancer diagnosis and treatment. Amenorrhea following adjuvant chemotherapy is not a reliable indicator of postmenopausal status. Patients who most clearly fit a postmenopausal definition are as follows: had bilateral oophorectomy; are amenorrheic and 60 years of age or older; or are age less than 60

but are amenorrheic for 12 or more consecutive months, in the absence of chemotherapy, endocrine therapy or ovarian function suppression, and who have FSH and estradiol levels in the postmenopausal range. Patients who do not clearly fit either the pre or postmenopausal definitions as outlined above are of uncertain menopausal status, as should be initially treated as premenopausal.

6. Some premenopausal patients will be offered ovarian function suppression with an LHRH agonist and hence will become eligible for AI therapy and bisphosphonates (see next section).
7. Aromatase inhibitor options include anastrozole and letrozole which are nonsteroidal AIs, and exemestane which is a steroidal AI.
8. Patients intolerant of initial AI may be switched to an alternate AI or tamoxifen. (*Level of Evidence: I, Strength of Recommendation: A*)

Bone Modifying Agents

1. Consider adjuvant bisphosphonate therapy (clodronate 1600 mg PO daily for 2-3 years or zoledronic acid 4 mg IV q6 months for 3-5 years) for postmenopausal patients (including premenopausal patients receiving ovarian function suppression) with lymph node positive or higher risk lymph node negative breast cancer (received adjuvant chemotherapy or eligible but unfit/declined).^{22, 23} (*Level of Evidence: I, Strength of Recommendation: A*)
2. Lower risk patients, or patients declining clodronate or zoledronic acid, may be offered other bisphosphonates or denosumab for management of low bone mass/fracture risk as per bone health guidelines.²⁴ (*Level of Evidence: I, Strength of Recommendation: A*)
3. Patients receiving ovarian function suppression (OFS), an aromatase inhibitor (AI), and/or a bone modifying agent, should be advised to supplement with calcium (1000 mg total dietary plus supplementation) and vitamin D (1000-2000 IU) per day. (*Level of Evidence: I, Strength of Recommendation: A*)
4. For any patient initiating a bone modifying agent, recommend dental evaluation prior to starting and preventive care for rare complication of osteonecrosis of the jaw.²⁵ (*Level of Evidence: V, Strength of Recommendation: A*)

Recommendations for Men with Early Breast Cancer¹

1. The approach to systemic therapy for men with early breast cancer is largely extrapolated from the literature to date based on female patients.
2. Chemotherapy and anti-HER2 therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients. (*Level of Evidence: V, Strength of Recommendation: A*)
3. However, for adjuvant hormonal therapy, tamoxifen is the standard of care. If there is a strong contraindication to tamoxifen, then an aromatase inhibitor in combination with an LHRH agonist can be considered. (*Level of Evidence: V; Strength of Recommendation: A*)

Figure 1. Approach to OncotypeDX testing in Alberta

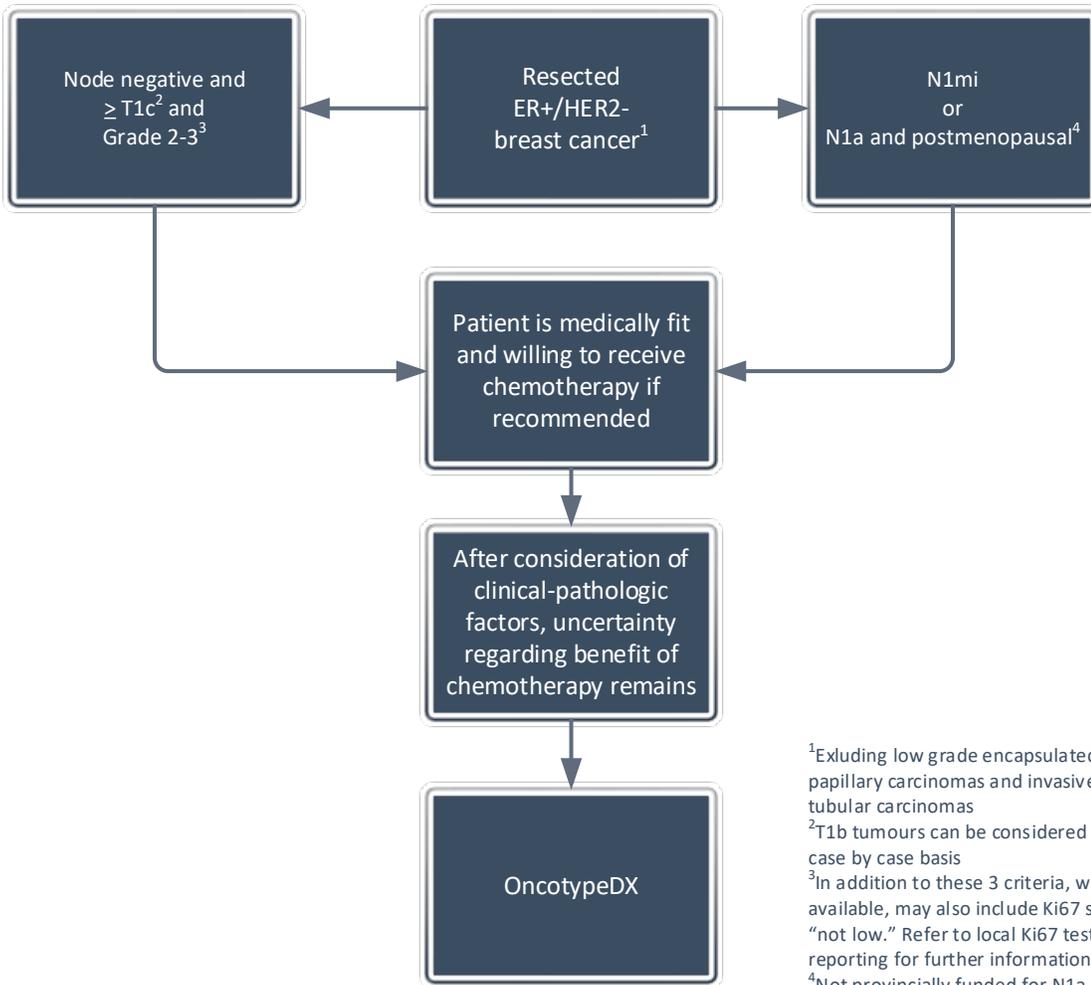


Figure 2. Approach to Adjuvant/Neoadjuvant Chemotherapy for HR+/HER2- Breast Cancer^{1, 2, 4-9, 26}

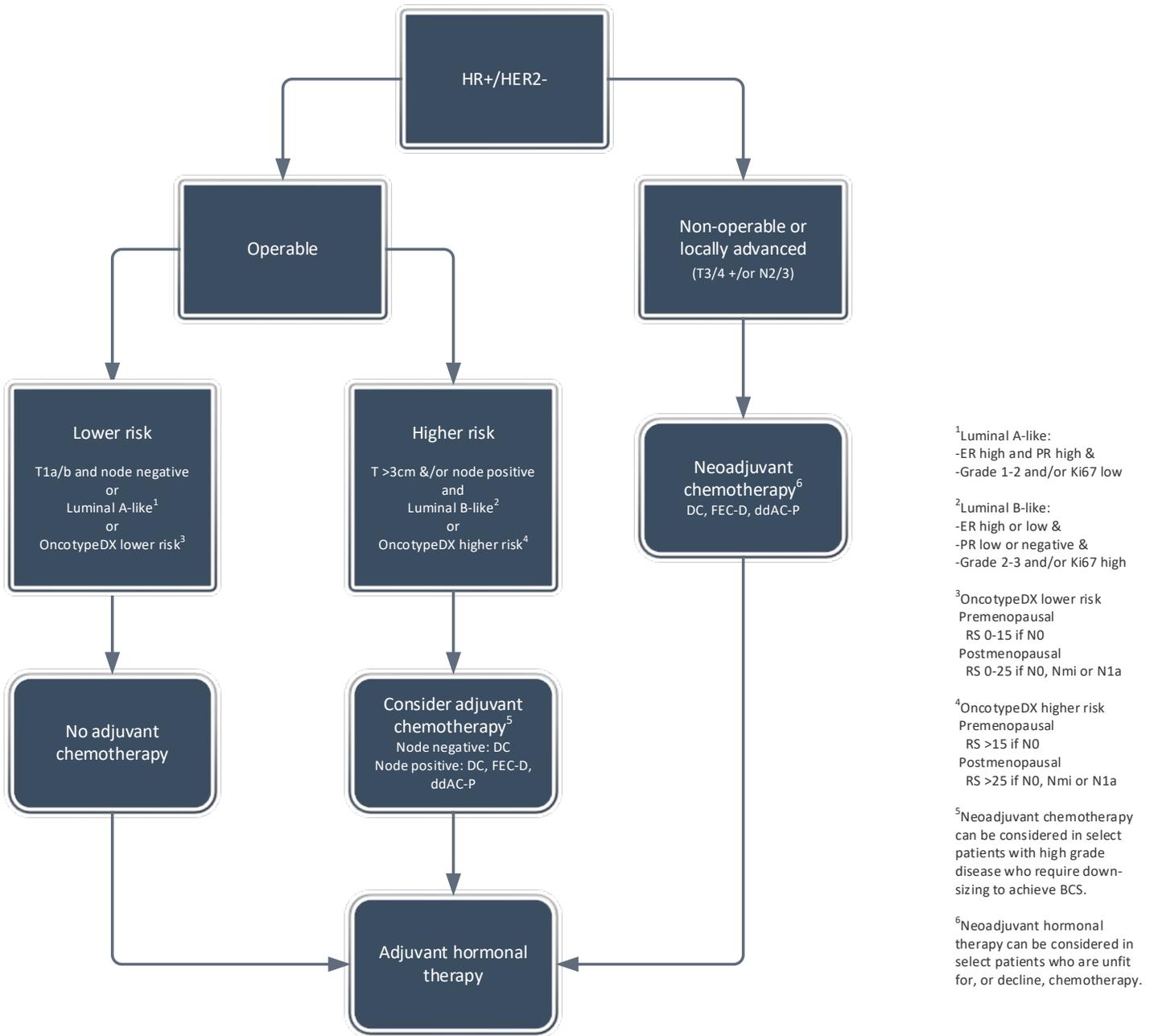
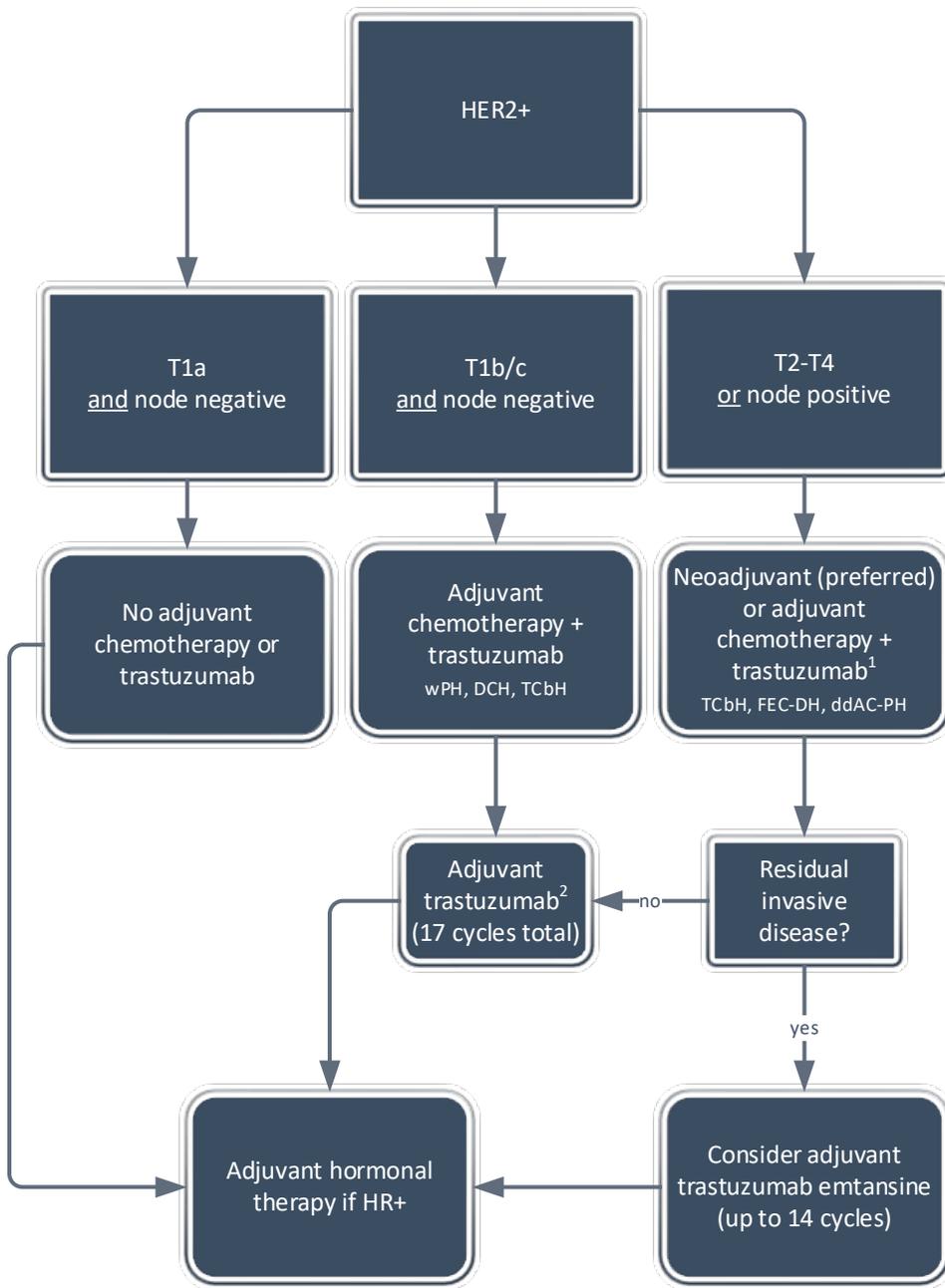


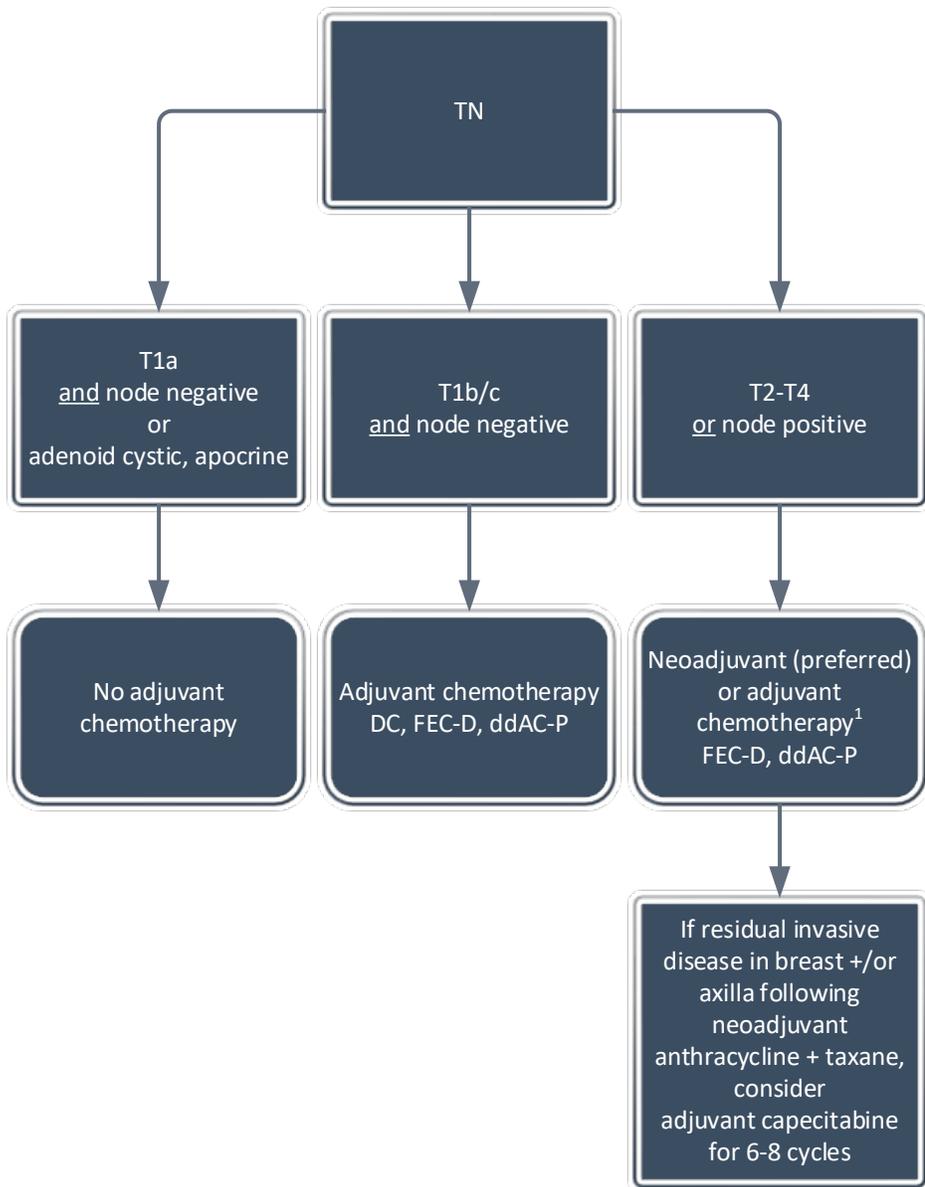
Figure 3. Approach to Adjuvant/Neoadjuvant Chemotherapy for HER2+ Breast Cancer^{1, 2, 6-9}



¹Addition of pertuzumab to trastuzumab in neoadjuvant setting increases pCR rate. Not provincially funded

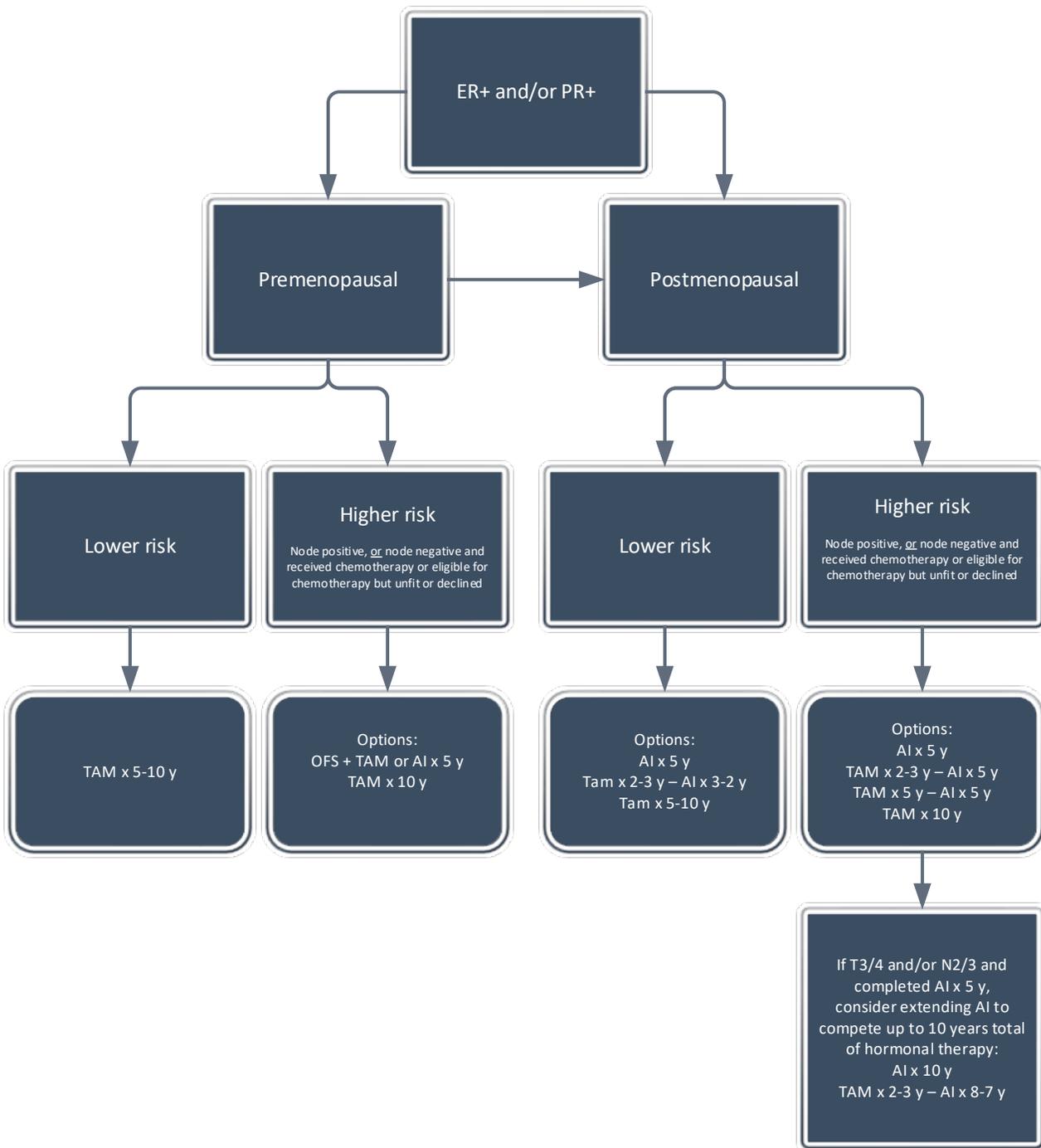
²Adjuvant pertuzumab plus trastuzumab compared with trastuzumab alone is associated with a small DFS benefit if node positive. Not provincially funded. In patients who have not received pertuzumab or trastuzumab emtansine, extended antiHER2 therapy with neratinib is associated with a small DFS benefit if higher risk, hormone receptor positive. Not provincially funded.

Figure 4. Approach to Adjuvant/Neoadjuvant Chemotherapy for Triple Negative (TN) Breast Cancer¹, 2, 6-9



¹The addition of a platinum to taxane component of regimen increases pCR rate. Impact on DFS/OS for overall population not proven. Can be discussed in select, motivated patients.

Figure 5. Approach to Adjuvant Hormonal Therapy^{1, 2, 19, 20}



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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in April 2014 and updated in April 2021.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally, not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AI, aromatase inhibitor; AJCC, American Joint Committee on Cancer; DC, docetaxel and cyclophosphamide; DCH, docetaxel, cyclophosphamide, trastuzumab; ddAC-P, dose-dense doxorubicin, cyclophosphamide followed by dose-dense paclitaxel; ddAC-PH, dose-dense doxorubicin, cyclophosphamide followed by dose-dense paclitaxel and trastuzumab; DFS, disease-free survival; ER, estrogen receptor; FEC-D, fluorouracil, epirubicin, cyclophosphamide followed by docetaxel; FEC-DH, fluorouracil, epirubicin, cyclophosphamide followed by docetaxel and trastuzumab;

GCSF, granulocyte colony-stimulating factor; GEP, gene expression profile; HER2, human epidermal growth factor 2); HR, hormone receptor; LHRH, luteinizing hormone-releasing hormone; OFS, ovarian function suppression; OS, overall survival; PR, progesterone receptor; RS, recurrence score; TAM, tamoxifen; TCbH, docetaxel, carboplatin, trastuzumab, TN, triple negative; wPH, weekly paclitaxel, trastuzumab

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Sasha Lupichuk reports consultancy/honoraria/research grants from Astra Zeneca, Eisai, Genomic Health, Myriad, Novartis, Pfizer.

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