Guideline Resource Unit
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Systemic Therapy for Non-Metastatic Breast Cancer: A Quick Reference

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Cancer Care Alberta

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Recommendations

Levels of evidence and grades of recommendation have been applied using the system shown on the last page of this guideline, which are then displayed in square brackets following each recommendation.

Chemotherapy for Non-Metastatic Breast Cancer

1. The decision for adjuvant or neoadjuvant chemotherapy (NAC) should be guided by the subtype of breast cancer, prognosis, benefits (absolute gains in disease free survival [DFS] and overall survival [OS]), toxicity risks, overall health of the patient, and patient preference [I, A].[1,2] Breast cancer subtypes include hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive, and triple negative (TN).
2. Individualized prognosis and expected benefit from systemic treatments, including chemotherapy, can be estimated using an online calculator like Predict Breast which considers factors such as patient's age and menopausal status, method of presentation (screen-detected or symptomatic), tumour size, axillary lymph node status, and the status of estrogen receptor (ER), HER2 and Ki67 if known.[3] In some patients with HR-positive/HER2-negative early breast cancer, prognosis and the potential benefit of chemotherapy can be estimated from gene expression profile (GEP) testing.[4,5] Figure 1 outlines the eligibility criteria for OncotypeDX testing in Alberta.
3. Figure 2 provides a decision-making approach for chemotherapy and other systemic therapy for HR-positive/HER2-negative breast cancer. Figure 3 covers HER2-positive breast cancer, and Figure 4 addresses triple negative breast cancer (TNBC) [I, A].[1,2,6-9]
4. When deciding on a chemotherapy regimen, considerations should include the patient's prognosis, the benefits (absolute gains in DFS and OS where applicable), toxicity risks, overall health, and patient preferences. Besides the listed chemotherapy regimens, other evidence-based options are available, and may be selected based on clinical discretion and/or review by a multidisciplinary breast cancer tumour board.
5. For patients with known cardiac dysfunction or significant cardiac risk, a non-anthracycline adjuvant chemotherapy regimen is preferred. If trastuzumab is needed in these patients, consider an upfront referral to cardiology.[10-12]
6. Delays in starting adjuvant chemotherapy should be avoided.[13] Adjuvant chemotherapy should begin as soon as surgical healing is complete, ideally within 12 weeks after surgery [I, A].[1]
7. Use primary granulocyte colony-stimulating factor (GCSF) prophylaxis with dose-dense regimens and those where the risk of febrile neutropenia is 20% or higher.[14] Use secondary GCSF prophylaxis if a neutropenic complication occurred in a previous chemotherapy cycle and if dose reduction is expected to compromise oncologic outcomes [I, A].[14]

Chemotherapy for HR-Positive/HER2-Negative Breast Cancer

1. Figure 2 outlines the recommended approach to systemic therapy for non-metastatic HR-positive/HER2-negative breast cancer [I, A].

2. Decision-making about chemotherapy in this group is complex due to the wide range of prognoses at each stage, driven by the underlying tumour biology. The American Joint Committee on Cancer (AJCC) 8th Edition includes prognostic stage grouping and considers not only T-stage and N-stage, but also tumour grade, ER-status, progesterone receptor (PR)-status, and the OncotypeDX Recurrence Score (RS) (if <11) when available.[15]
3. Consider favourable tumour biology when a luminal A molecular signature or luminal A-like characteristics are present, indicated by high ER and PR expression AND grade 1-2 and/or low Ki67 score).[1,2]
4. Consider less favourable tumour biology when a luminal B molecular signature or luminal B-like characteristics are present, indicated by high or low ER expression AND low PR expression or PR-negative AND grade 2-3 and/or higher Ki67 score.[1,2]
5. For patients with favourable tumour biology, the predicted absolute benefit in OS from chemotherapy is typically low. However, for those with less favourable tumour biology, the predicted absolute benefit in OS from chemotherapy can vary considerably. Predict Breast[3], and in eligible patients, OncotypeDX testing, can aid in prognostication and guiding chemotherapy decisions [I, A].[16,17]

Chemotherapy and Targeted Therapies for HER2-Positive Breast Cancer

1. Figure 3 outlines the recommended systemic therapy approach for non-metastatic HER2-positive breast cancer [I, A].
2. All patients with HER2-positive breast cancer requiring adjuvant or neoadjuvant chemotherapy should be considered for the addition of trastuzumab, administered for up to a total duration of 1 year [I, A]. Trastuzumab in these patients reduces the risk of breast cancer recurrence and breast cancer-related mortality by approximately one-third in relative terms for each outcome.[18]
3. *Pertuzumab* in addition to trastuzumab may be considered in patients with resected node-positive disease who will receive adjuvant chemotherapy and in patients who require NAC [I, A]. Pertuzumab in addition to trastuzumab has not definitively shown a mortality benefit in the curative setting. According to the APHINITY study, patients with HER2-positive/node-positive (but not node-negative) disease who did not receive neoadjuvant therapy experienced a 5% improvement in invasive disease-free survival (iDFS) at 8 years when pertuzumab was added to adjuvant chemotherapy and trastuzumab.[19] The HR-positive subgroup benefited similarly to the HR-negative subgroup. Pertuzumab plus neoadjuvant trastuzumab and chemotherapy increases the rate of achieving pathological complete response (pCR).[20,21] Achieving pCR allows for potential de-escalation of local management and post-operative systemic therapies [I, A]. Continuation of pertuzumab with trastuzumab in the adjuvant setting for those who had clinical or pathological node positive disease who achieve a pCR with NAC is supported in some guidelines but not others.[22,23]*

* As of February 11, 2025, according to the Alberta Health Service (AHS) Outpatient Cancer Drug Benefit Program, pertuzumab is not provincially funded for breast cancer treatment in the adjuvant or neoadjuvant setting.

4. Patients with residual invasive disease in the breast or axilla after neoadjuvant anti-HER2 therapy plus chemotherapy should be considered for adjuvant treatment with trastuzumab emtansine for up to 14 cycles [I, A]. According to the Katherine trial, compared to trastuzumab alone, trastuzumab emtansine improved iDFS by 13.7% and OS by 4.7% at 7 years.[24]
5. *Based on findings from the ExteNET study, neratinib* for one year may be considered following completion of trastuzumab-based neoadjuvant or adjuvant therapies in HER2-positive, HR-positive disease that is higher risk (e.g., stage II/III and did not achieve pCR after NAC).[25-27] [I, B] Patients showed a modest 2.5% improvement in iDFS at 5 years. The iDFS benefit was 5.1% if neratinib was initiated </= 1 year of trastuzumab completion but only 1.3% if neratinib was initiated beyond 1 year of trastuzumab completion. OS results were not significant overall. However, there was a 9.1% OS benefit at 8 years observed for the post NAC patients with residual disease and early initiation of neratinib. It's important to note that participants in the ExteNET study had not previously received neoadjuvant or adjuvant pertuzumab, or adjuvant trastuzumab emtansine if residual disease was present.*

Chemotherapy and Immunotherapy for TNBC

1. Figure 4 outlines the recommended approach to systemic therapy for non-metastatic TNBC [I, A].
2. Based on findings from the Keynote-522 study, pembrolizumab should be considered in combination with NAC (carboplatin plus paclitaxel for 4 cycles followed by doxorubicin or epirubicin with cyclophosphamide for 4 cycles) for patients with TNBC, with at least clinical stage T2 and/or N1 disease, regardless of PDL1 status.[28-30] In Keynote-522, pembrolizumab was continued every 3 weeks after definitive surgery for up to 9 cycles irrespective of pCR. The study showed a pCR benefit of 13.6% and an event-free survival (EFS) benefit of 9% at 5 years. In terms of OS, there was a 4.9% benefit at 5 years for the intention-to-treat population. The OS benefit was numerically greater in patients who did not have a pCR in comparison to those that did have a pCR (6.1% vs 0.7%).
    - Residual invasive disease/no pCR: Neither adjuvant capecitabine nor olaparib (for germline BRCA mutation carriers) were permitted in the Keynote-522 trial. Therefore, the impact of combining capecitabine or olaparib with adjuvant pembrolizumab on long term outcomes remains unknown. In the setting of pembrolizumab toxicity/discontinuation, adjuvant capecitabine for 6-8 cycles can be considered. In the CREATE-X trial, for patients with residual disease post NAC, there was an OS benefit of 8.5% at 5 years. Alternatively, if the patient has a germline BRCA mutation, adjuvant olaparib for 1 year can be used (see later section).
    - No residual invasive disease/pCR: As Keynote-522 was not designed to discern the relative efficacy contributions of the neoadjuvant and adjuvant treatment phases, continuation of pembrolizumab in the adjuvant setting should still be considered.

* As of February 11, 2025, according to the AHS Outpatient Cancer Drug Benefit Program, neratinib is not provincially funded for breast cancer treatment.

Hormonal Therapy

1. Adjuvant hormonal therapy should be considered for all patients who have undergone resection for HR-positive early breast cancer [I, A].[1,2,31,32]
2. The decision to proceed with adjuvant hormonal therapy and the choice of regimen should be guided by prognosis, potential benefits (absolute gains in DFS and OS where applicable), toxicity risks, overall health of the patient, and patient preference [I, A].[1,2,31,32]
3. As for the case of chemotherapy, individualized prognosis and expected benefit from hormonal therapy can be estimated using an online calculator like Predict Breast or "working backwards" from distant recurrence risk provided through OncotypeDX testing if available. For premenopausal women, the Composite Risk Application can be used to estimate the benefit of adding in ovarian function suppression (OFS) to tamoxifen and for comparing OFS + exemestane versus OFS + tamoxifen.[33]
4. Figure 5 outlines a decision-making approach for hormonal therapy in HR-positive/HER2-negative breast cancer [I, A].[1,2,31,32]
5. Menopausal status:[34] Patients are clearly premenopausal if they have 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 clearly fit the postmenopausal definition include those who have had a bilateral oophorectomy, are amenorrheic and 60 years or older, or under 60 but have been amenorrheic for 12 or more consecutive months (without chemotherapy, endocrine therapy, or ovarian function suppression) and have follicle-stimulating hormone (FSH) and estradiol levels in the postmenopausal range. Patients who do not clearly fit either the premenopausal or postmenopausal definitions are considered to have uncertain menopausal status and should initially be treated as premenopausal.
6. Some premenopausal patients may be offered ovarian function suppression with a luteinizing hormone-releasing hormone (LHRH) agonist, making them eligible for aromatase inhibitor (AI) therapy and bisphosphonates (see next section).
7. The POSITIVE study indicated that temporarily interrupting adjuvant hormonal therapy after 18-30 months is safe in terms of short-term breast cancer outcomes for premenopausal patients with predominantly stage I or II HR-positive/HER2-negative breast cancer.[35] The study required a 3-month wash-out period before attempting pregnancy, and the fertility trial lasted for up 2 years [III, A].
8. For postmenopausal patients with higher risk disease, extended adjuvant hormonal therapy beyond 5 years using an AI is estimated to offer a 2-4% DFS benefit without improvement in overall survival.[32] The literature to date suggests that total duration of therapy of 7-8 years is sufficient for most with inclusion of an AI.[23,32]
9. AI options include anastrozole and letrozole, which are nonsteroidal AIs, or exemestane, a steroidal AI. Choice may be influenced by individual patient factors and preferences. Patients who are intolerant of their initial AI may be switched to an alternate AI or tamoxifen.

CDK4/6 Inhibitors

1. Based on the results of the monarchE study, adjuvant abemaciclib combined with hormonal therapy should be considered for patients with resected lymph node-positive, HR-positive/HER2-negative breast cancer who are at high risk of recurrence. This includes those with ≥4 positive axillary nodes, or 1-3 positive axillary nodes plus a tumour size ≥5 cm, grade 3, or Ki-67 ≥20%.[36-38] The recommended duration for abemaciclib is 2 years, starting within 16 months of surgical resection and within 3 months of initiating adjuvant hormonal therapy. The study showed a 7.6% improvement in iDFS and a 6.7% improvement in distant relapse-free survival (DRFS) at 5 years. While there have been numerically fewer deaths relating to breast cancer in the abemaciclib arm, the OS data is immature [I, A].
2. *Adjuvant ribociclib[‡] is an emerging option for a broader range of patients as per the NATALLEE trial. Patients had resected, HR-positive/HER2-negative breast cancer with: T3/T4 and/or node positive disease. Patients with T2N0 tumours plus grade 3 or grade 2 with a Ki-67 >/= 20% and/or a high-risk genomic profile score (i.e. OncotypeDX RS >/= 26) were also included. Adding ribociclib to a non-steroidal AI for 3 years resulted in a 4.9% improvement in iDFS 4 years. DDFS was also improved with OS data yet immature.[39]*

PARP Inhibitors

According to the OlympiA study, patients with pathogenic variants in BRCA1 or BRCA2 who have resected HER2-negative, higher risk, breast cancer, and have undergone neoadjuvant or adjuvant chemotherapy can be offered adjuvant olaparib for 1 year (concurrent with hormonal therapy if HR-positive) [I, A].[40-43] At 6 years, there was a 9.4% benefit in iDFS, a 7.8% benefit in DDFS, and a 4.4% benefit in OS. For HR-positive disease, patients must have had ≥4 positive nodes or a clinical and pathologic stage [CPS] and ER status and histologic grade [EG] score >3 post NAC. Patients with TNBC had resected T2-T4N0 or N1 tumours or residual disease post-NAC. Post-NAC patients were not allowed any chemotherapy in the adjuvant setting. The OlympiA study did not include patients exposed to adjuvant CDK4/6 inhibitors or neoadjuvant/adjuvant immunotherapy.

Bisphosphonates

Consider adjuvant bisphosphonate therapy for postmenopausal patients (including premenopausal patients receiving ovarian function suppression) with lymph node-positive or higher-risk lymph node-negative breast cancer. Evidence-based regimens include *clodronate 1600 mg orally daily for 2-3 years*, zoledronic acid 4 mg intravenously every 6 months for 3 years or *zoledronic acid 4 mg every 3 months for 2 years* [I, A].[*44-46] As for all systemic therapies, the decision to proceed with an adjuvant

[‡] As of February 11, 2025, according to the AHS Outpatient Cancer Drug Benefit Program, ribociclib is not provincially funded for patients with breast cancer in the adjuvant setting.
[*] As of February 11, 2025, according to the AHS Outpatient Cancer Drug Benefit Program, oral clodronate and zoledronic acid every 3 months are not provincially funded.

bisphosphonate should be guided by prognosis, potential benefits, toxicity risks, overall health of the patient, and patient preference.

Fertility

1. Refer to the oncofertility recommendations in Cancer Care Alberta's Adolescent and Young Adult (AYA) Cancer guideline for direction on discussing the impact of therapy on fertility, referral to a fertility clinic, contraception, and pregnancy testing.[47]
2. *If standard fertility preservation methods are not feasible or in addition to these methods, the use of an LHRH[t] agonist during chemotherapy can be considered to reduce the risk of chemotherapy-induced ovarian insufficiency [II, B].*[48,49]

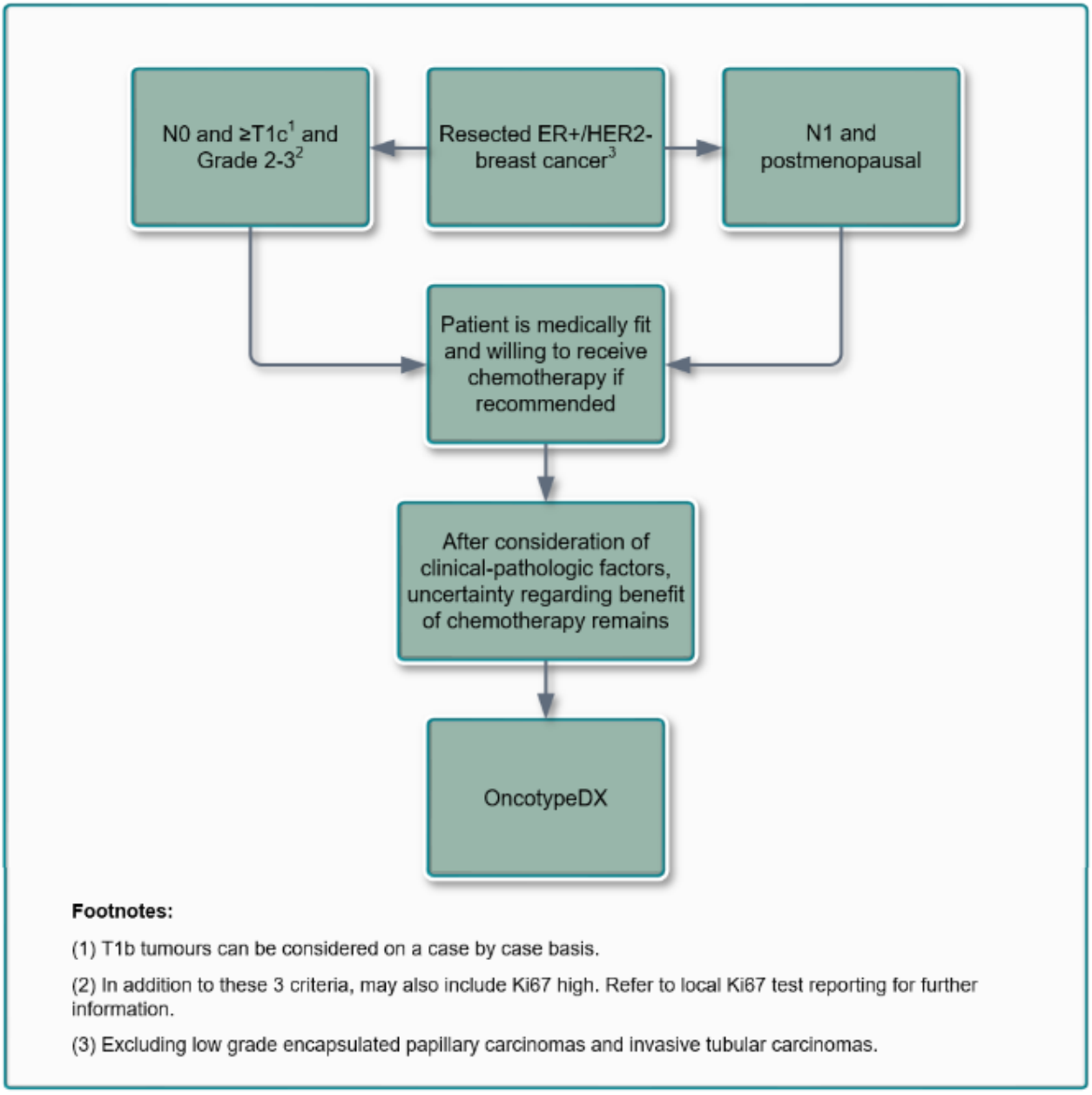
Recommendations for Men

The approach to systemic therapy for men with early breast cancer is primarily based on literature and research on female patients.

1. Chemotherapy and targeted therapy indications and regimens for male breast cancer should follow the same recommendations as those for female breast cancer patients [V, A].
2. For adjuvant hormonal therapy, tamoxifen is the standard of care. If tamoxifen is strongly contraindicated, an AI in combined with an LHRH agonist can be considered as an alternative [I, A].

[t] As of February 11, 2025, according to the AHS Outpatient Cancer Drug Benefit Program, LHRH agonists are not provincially funded for use during chemotherapy for the purpose of ovarian protection.

Figure 1. Approach to OncotypeDX testing in Alberta



Footnotes:

(1) T1b tumours can be considered on a case by case basis.

(2) In addition to these 3 criteria, may also include Ki67 high. Refer to local Ki67 test reporting for further information.

(3) Excluding low grade encapsulated papillary carcinomas and invasive tubular carcinomas.

Figure 2. Approach to Systemic Therapy for Non-Metastatic HR+/HER2- Breast Cancer[1,2,4-9,50]

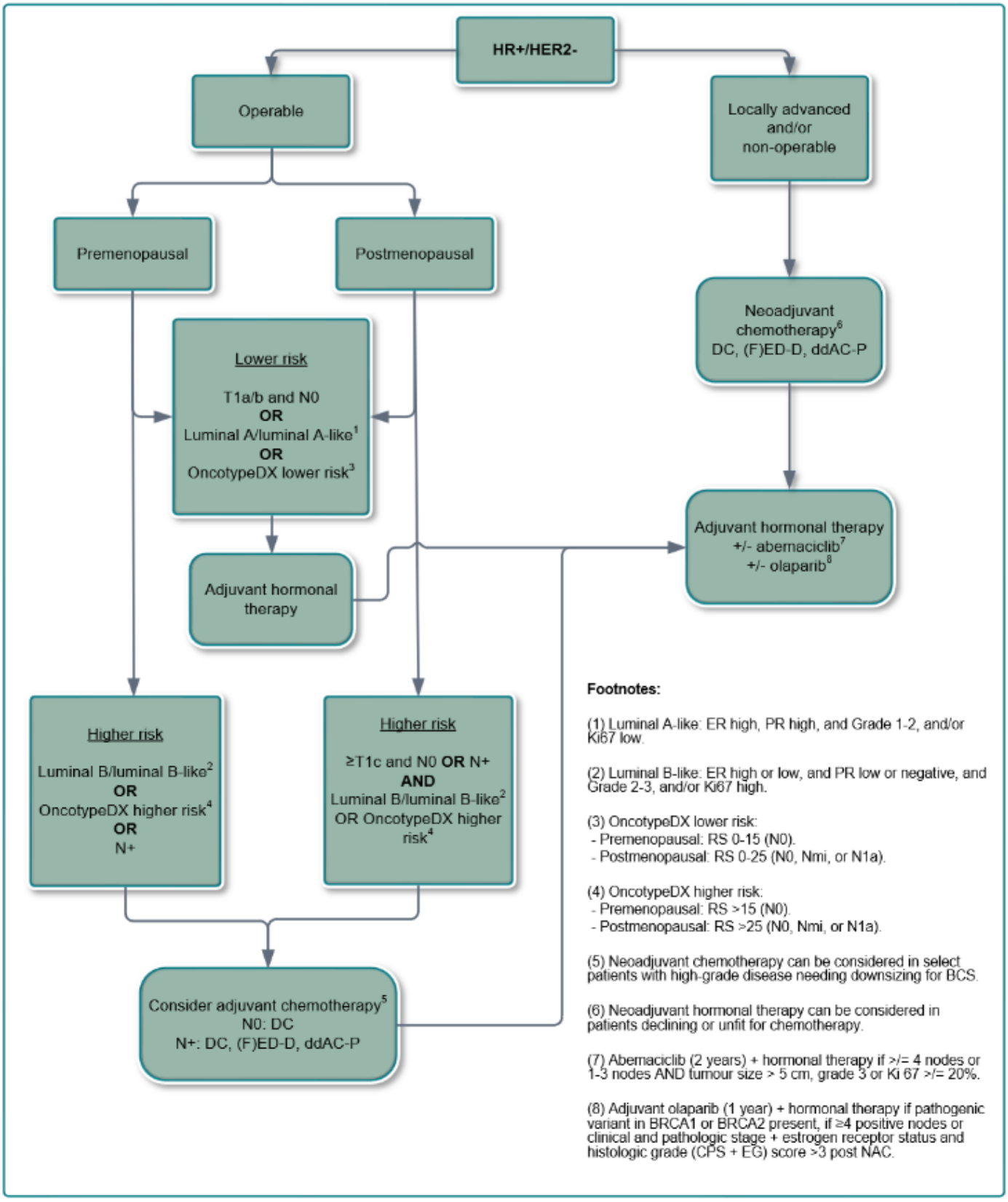
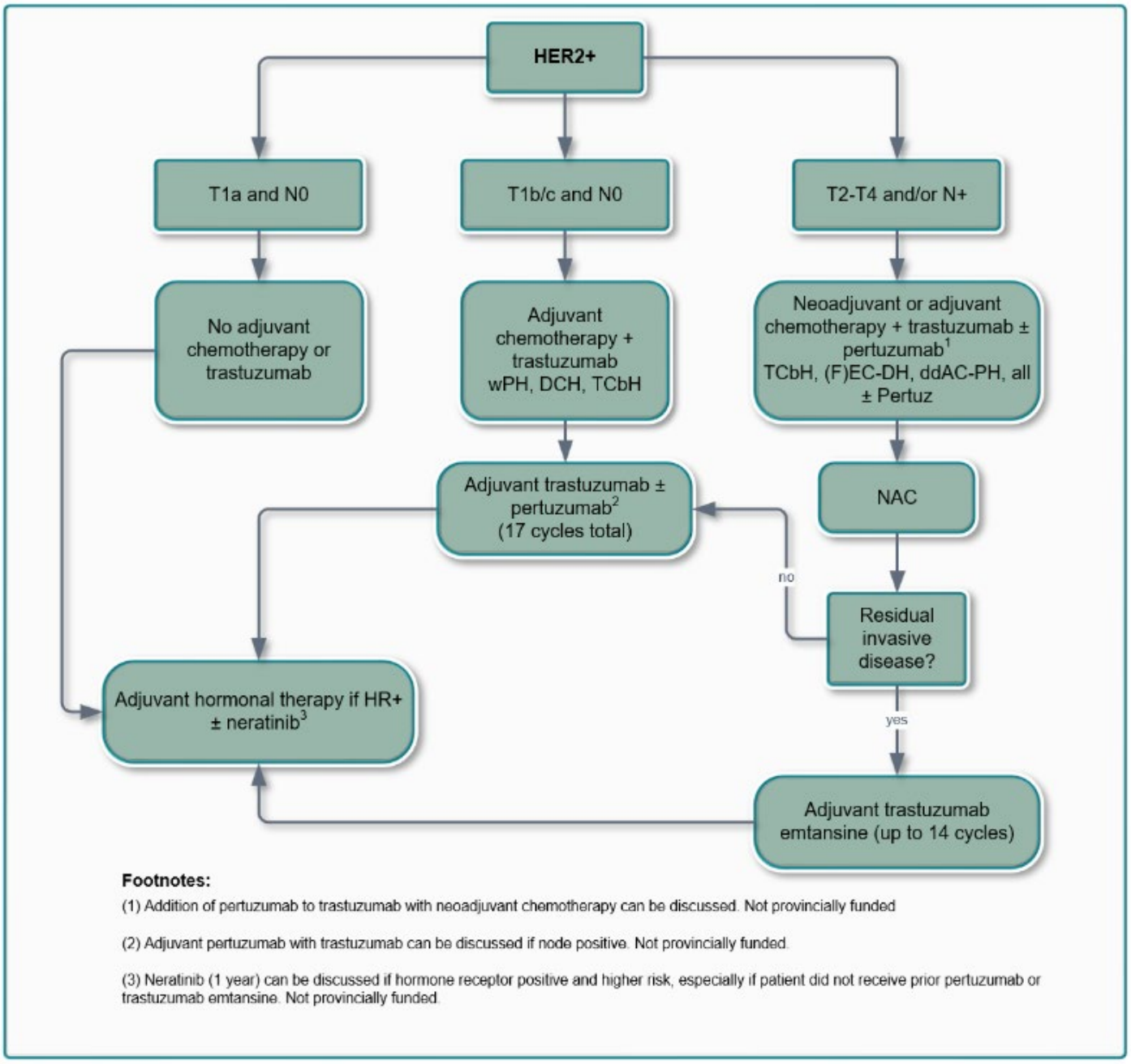


Figure 3. Approach to Systemic Therapy for Non-Metastatic HER2+ Breast Cancer[1,2,6-9]



Footnotes:

(1) Addition of pertuzumab to trastuzumab with neoadjuvant chemotherapy can be discussed. Not provincially funded

(2) Adjuvant pertuzumab with trastuzumab can be discussed if node positive. Not provincially funded.

(3) Neratinib (1 year) can be discussed if hormone receptor positive and higher risk, especially if patient did not receive prior pertuzumab or trastuzumab emtansine. Not provincially funded.

Figure 4. Approach to Systemic Therapy for Non-Metastatic Triple Negative (TN) Breast Cancer[1,2,6-9]

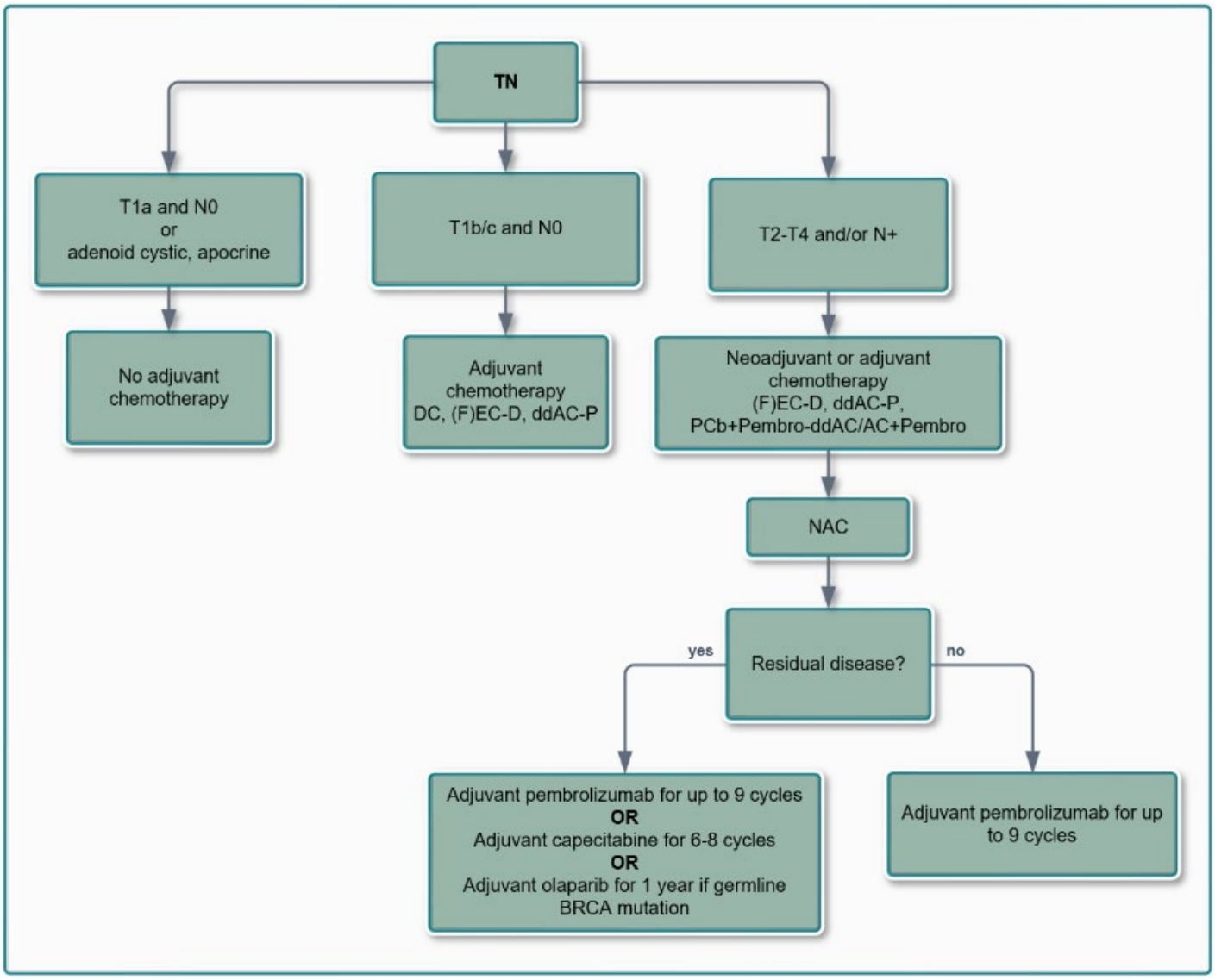
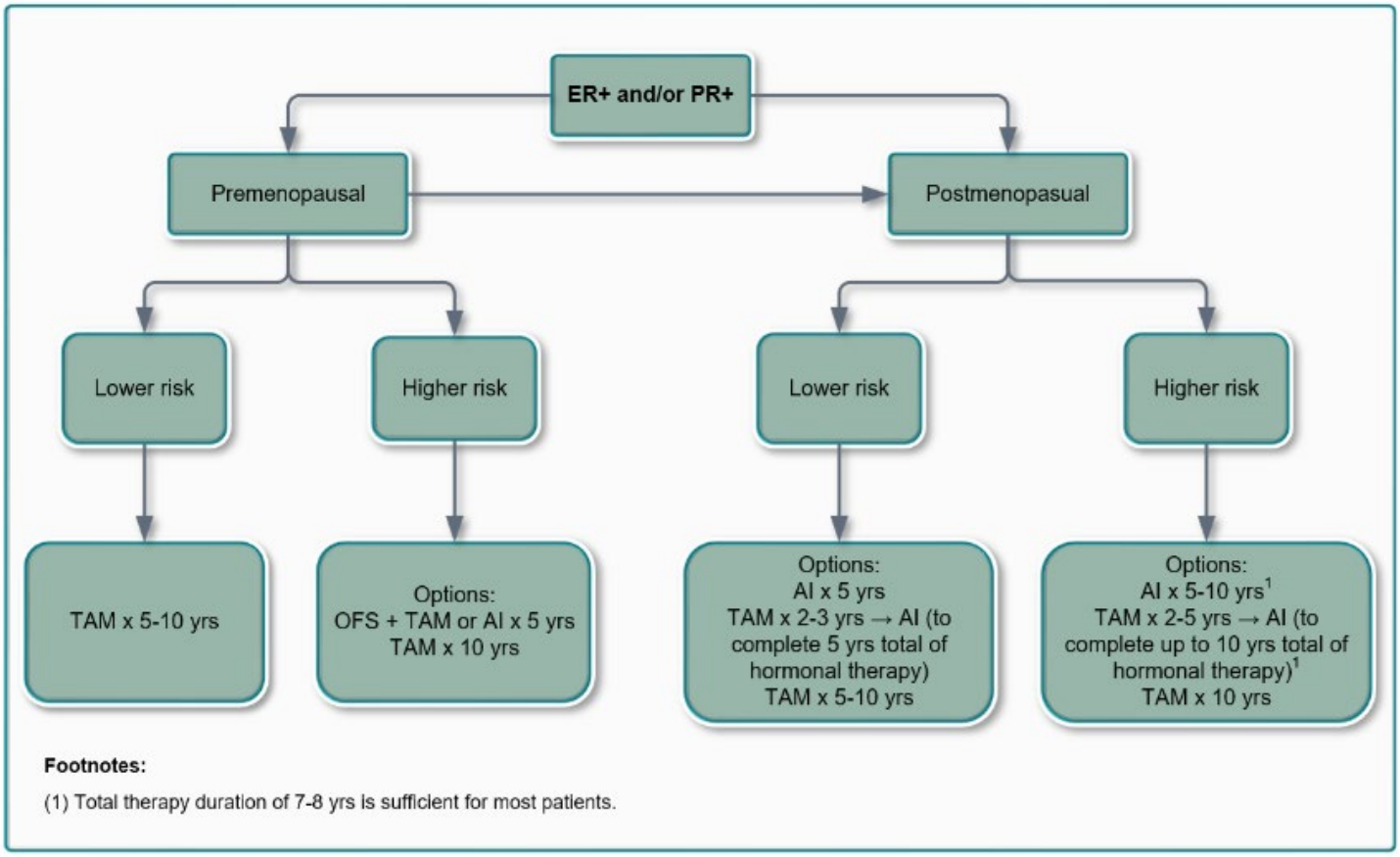


Figure 5. Approach to Adjuvant Hormonal Therapy[1,2,31,32]



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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 revised multiple times, most recently in February 2025.

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 2027. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AC, doxorubicin, cyclophosphamide; AHS, Alberta Health Services; AI, aromatase inhibitor; AJCC, American Joint Committee on Cancer; AYA, adolescent and young adult; CADTH, Canadian Agency for Drugs and Technologies in Health; CPS, clinical and pathologic stage; D, docetaxel; dd, dose dense; DC, docetaxel, cyclophosphamide; DCH, docetaxel, cyclophosphamide, trastuzumab; DH, docetaxel, trastuzumab; DFS, disease-free survival; DRFS, distant relapse-free survival; EG, ER status and histologic grade; ER, estrogen receptor; FEC, fluorouracil, epirubicin, cyclophosphamide; FSH, follicle-stimulating hormone; GCSF, granulocyte colony-stimulating factor; GEP, gene expression profile; HER2, human epidermal growth factor 2; HR, hormone receptor; iDFS, invasive disease-free survival; LHRH, luteinizing hormone-releasing hormone; NAC, neoadjuvant chemotherapy; OS, overall survival; P, paclitaxel; pCR, pathologic complete response; PH, paclitaxel, trastuzumab; PCb, paclitaxel, carboplatin; Pertuz, pertuzumab; PR, progesterone receptor; RS, recurrence score; TCbH, docetaxel, carboplatin, trastuzumab; TNBC, triple negative breast cancer.

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, Medical Oncologist, reports receiving institutional grants or contracts from Pfizer and serving as a local principal investigator or sub-investigator on multiple industry-sponsored clinical trials.
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