

# Adjuvant Systemic Therapy for Early Stage (Lymph Node Negative and Lymph Node Positive) Breast Cancer

Effective Date: April, 2018



## Recommendations

### Overarching Recommendations for Patients with Breast Cancer

Adjuvant chemotherapy should start preferably within 60 days after surgery,<sup>1</sup> and is not recommended more than 12 weeks after surgery.<sup>2</sup>

### Systemic Therapy Recommendations for Lymph Node Negative Breast Cancer

**Table 1. Risk Categories for Lymph Node Negative Breast Cancer**

Risk Category	Risk Factor <sup>3</sup>
Adverse Prognostic Factors	<ul style="list-style-type: none"> <li>• Age &lt; 35 years</li> <li>• HER2 over-expression (HER2+)</li> <li>• Presence of lymphovascular invasion</li> <li>• Grade 3</li> <li>• Hormone receptor negative disease</li> <li>• Genomic test score:* higher risk<sup>3-5</sup></li> </ul>
Lower Risk	<ul style="list-style-type: none"> <li>• ≤ 2 cm, grade 1, with no other adverse prognostic factors</li> <li>• &lt; 0.5 cm with any other feature</li> <li>• Genomic test score:* lower risk<sup>3-5</sup></li> </ul>
Intermediate Risk	<ul style="list-style-type: none"> <li>• All other combinations of factors that do not fit into either the low or high risk criteria</li> <li>• Genomic test score:* intermediate risk<sup>3-5</sup></li> </ul>
Higher Risk	<ul style="list-style-type: none"> <li>• &gt; 1 cm with any 2 or more adverse prognostic factors</li> <li>• &gt; 2 cm with any 1 or more adverse prognostic factors</li> <li>• &gt; 3 cm +/- adverse prognostic factors</li> <li>• Special Considerations for HER2+ breast cancer (See Table 4)</li> <li>• Genomic test score:* higher risk<sup>3-5</sup></li> </ul>

\* Examples: Prosigna™, OncotypeDx®<sup>6</sup>

**Table 2. Genomic Testing for Systemic Therapy Decision Making\*<sup>3-5</sup>**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>• Patient is medically fit to receive adjuvant breast cancer chemotherapy</li> </ul> <p style="text-align: center;"><b>AND</b></p> <ul style="list-style-type: none"> <li>• Has early stage resected lymph node negative (including N0i+) or N1mi</li> </ul> <p style="text-align: center;"><b>AND</b></p> <ul style="list-style-type: none"> <li>• Either grade 2 or grade 3 invasive breast cancer</li> </ul>	<ul style="list-style-type: none"> <li>• Patients unwilling to consider or are medically unfit to receive adjuvant breast cancer chemotherapy</li> <li>• Lymph node positive breast cancer</li> <li>• Metastatic breast cancer</li> <li>• HER2 positive breast cancer</li> <li>• Grade 1 invasive breast cancer (see note*)</li> </ul>
<p><b>Special considerations, however, may apply, based on multidisciplinary breast cancer tumour board review.</b></p>	

\* Examples: Prosigna™, OncotypeDx®<sup>6</sup>

**Table 3. Treatment Recommendations for Lymph Node Negative Breast Cancer**

	Hormone Receptor Positive (+)	Hormone Receptor Negative (-)	HER2 Positive (+)
Lower Risk	Observation* OR Hormonal Therapy	Observation	See Table 4
Intermediate Risk	Hormonal Therapy +/- Chemotherapy	Chemotherapy	
Higher Risk	Chemotherapy + Hormonal Therapy	Chemotherapy	
<b>Consider/discuss bisphosphonate for 3-5 years as adjuvant therapy for postmenopausal patients with higher risk lymph node negative breast cancer.</b> <sup>7,8</sup>			

\* Systemic therapy may NOT be offered to patients in cases where the patient has other significant co-morbidities which precludes the safe administration of adjuvant systemic therapy, and/or the patient has limited life expectancy.

**Table 4. Chemotherapy Options for Lymph Node Negative Breast Cancer**

HER2(-) Lymph Node(-)	
Lower risk:	No adjuvant chemotherapy recommended
Intermediate risk:	CMF or AC, or DC <sup>9-11</sup>
Higher risk:	<ul style="list-style-type: none"> <li>DC<sup>11</sup></li> <li>FEC-D or other phase III evidence-based sequential anthracycline-taxane regimens if hormone-receptor negative<sup>12,13</sup></li> </ul>
HER2(+) Lymph Node(-)	
<0.5 cm:	ER (+): discuss hormonal therapy
	ER (-): no adjuvant trastuzumab-based chemotherapy is generally recommended (special considerations may apply)
0.5 cm to 1 cm:	ER (+): discuss hormonal therapy +/- adjuvant trastuzumab-based chemotherapy
	ER (-): discuss adjuvant trastuzumab-based chemotherapy
>1 cm:	ER (+): discuss hormonal therapy and adjuvant trastuzumab-based chemotherapy
	ER (-): discuss adjuvant trastuzumab-based chemotherapy
<ul style="list-style-type: none"> <li>Anthracycline based options: FEC-DH<sup>14</sup> or other phase III evidence-based sequential anthracycline-taxane/trastuzumab regimens</li> <li>Non-anthracycline based option: docetaxel / carboplatin / trastuzumab (DCbH x 6)<sup>15</sup></li> <li>Other evidence-based treatment options exist and may be used based on clinical discretion and in review with multidisciplinary breast cancer tumour board</li> <li>Concurrent trastuzumab and taxane preferred over sequential chemotherapy-trastuzumab treatment regimens</li> </ul>	

<ul style="list-style-type: none"> <li>Cardiac risk factor concerns: consider Cardiology Review. Non-anthracycline treatment regimens are preferred<sup>16,17</sup></li> </ul> <p>Trastuzumab duration = 1 year (e.g. 17 x q3week cycles)<sup>18,19</sup></p>
<b>GCSF</b>
<ul style="list-style-type: none"> <li>Use according to clinical discretion and ASCO recommendations<sup>20</sup></li> </ul>

## Systemic Therapy Recommendations for Lymph Node Positive Breast Cancer

**Table 5. Treatment Recommendations for Lymph Node Positive Breast Cancer**

	Hormone Receptor (+)	Hormone Receptor (-)
HER2(-)	Chemotherapy + Hormonal Therapy	Chemotherapy
HER2(+)	Trastuzumab-based adjuvant chemotherapy + Hormonal Therapy	Trastuzumab-based adjuvant chemotherapy
<b>Consider/discuss bisphosphonate for 3-5 years as adjuvant therapy for postmenopausal patients.</b> <sup>7,8</sup>		
Systemic therapy may NOT be offered to patients in cases where: <ul style="list-style-type: none"> <li>N1mi, ER+, HER2-, genomic test score lower risk</li> <li>The patient has other significant co-morbidities which precludes the safe administration of adjuvant systemic therapy and/or the patient has limited life expectancy</li> </ul>		

**Table 6. Chemotherapy Options for Lymph Node Positive Breast Cancer**

<b>HER2(-) Lymph Node(+)</b>
<ul style="list-style-type: none"> <li>Anthracycline based options: <ul style="list-style-type: none"> <li>FEC-D<sup>21,22</sup> or other phase III evidence-based sequential anthracycline-taxane regimens</li> <li>TAC<sup>22,23</sup></li> </ul> </li> <li>Non-anthracycline based option: DC<sup>11</sup></li> </ul>
<b>HER2(+) Lymph Node (+)</b>
<ul style="list-style-type: none"> <li>Anthracycline based options: FEC-DH<sup>14</sup> or other phase III evidence-based sequential anthracycline-taxane/trastuzumab regimens</li> <li>Non-anthracycline based option: docetaxel / carboplatin / trastuzumab (DCbH x 6)<sup>15</sup></li> <li>Other evidence-based treatment options exist and may be used based on clinical discretion and in review with multidisciplinary breast cancer tumour board</li> <li>Concurrent trastuzumab and taxane preferred over sequential chemotherapy-trastuzumab treatment regimens</li> <li>Cardiac risk factor concerns: consider Cardiology Review. Non-anthracycline treatment regimens are preferred<sup>16,17</sup></li> <li>Trastuzumab duration = 1 year (e.g. 17 x q3week cycles)<sup>18,19</sup></li> </ul>

## GCSF

- Use according to clinical discretion and ASCO recommendations<sup>20</sup>

### Adjuvant Chemotherapy in the Setting of Residual Invasive Disease Post Neoadjuvant Anthracycline + Taxane

If triple negative disease (ER negative, PR negative, HER2 negative) AND residual invasive carcinoma in breast or lymph node(s), discuss potential benefits/risks associated with adjuvant capecitabine 1000-1250 mg/m<sup>2</sup> twice daily (starting dose) x 14 days q21 days for 6-8 cycles.<sup>24</sup>

The benefit of adjuvant capecitabine for hormone receptor positive disease is less compelling and remains unstudied for HER2 positive disease.

**Table 7. Adjuvant Hormonal Therapy for Hormone Receptor Positive Disease Only**

Patient Group	
Premenopausal	<p><b>Options:</b></p> <ul style="list-style-type: none"> <li>• Tamoxifen x 5-10 years<sup>7,25-28</sup></li> <li>• If higher risk and would ordinarily be advised to receive adjuvant chemotherapy, consider ovarian suppression with LHRH agonist plus tamoxifen or an aromatase inhibitor for 5 years. Women tolerating ovarian suppression with LHRH agonist may elect to have bilateral oophorectomy instead.<sup>7</sup></li> </ul>
Postmenopausal	<p><b>Options:</b></p> <ul style="list-style-type: none"> <li>• AI x 5 years<sup>29,30</sup> (preferred)</li> <li>• Tamoxifen x 2-3 years → AI x 2-3 years (total 5 years adjuvant hormonal therapy)<sup>29,30</sup></li> </ul> <p>Tamoxifen x 5-10 years if an AI is contraindicated<sup>28,29</sup></p> <p><b>Aromatase Inhibitor Intolerance:</b></p> <ul style="list-style-type: none"> <li>• A switch to an alternate AI may be considered or the patient could be switched to tamoxifen (provided that there is no contraindication to do so)<sup>30</sup></li> </ul>
Extended Adjuvant Therapy with an AI	<p><b>Options if higher risk node negative or node positive and have completed 5 years of adjuvant tamoxifen:</b><sup>28,31</sup></p> <ul style="list-style-type: none"> <li>• AI x 3-5 years</li> <li>• Additional 5 years of adjuvant tamoxifen, if an AI is contraindicated</li> </ul>
Aromatase Inhibitor Options:	<p><b>Non-steroidal:</b> Anastrozole or Letrozole<sup>29,32-34</sup></p> <p><b>Steroidal:</b> Exemestane<sup>33</sup></p>
<p><b>Menopausal Status</b><sup>35</sup></p> <ul style="list-style-type: none"> <li>• Patients are clearly premenopausal if they demonstrate regular menses without using oral contraception or hormone replacement therapy prior to breast cancer diagnosis and treatment. However, amenorrhea following adjuvant chemotherapy is not a reliable indicator of postmenopausal status.</li> <li>• Those patients that most clearly fit a postmenopausal definition are as follows: <ul style="list-style-type: none"> <li>• Patients who have had bilateral oophorectomy, or</li> <li>• Amenorrheic patients 60 years of age or older, or</li> </ul> </li> </ul>	

- Age less than 60 but are amenorrheic for 12 or more consecutive months, in the absence of chemotherapy, endocrine therapy or ovarian suppression and who have FSH and estradiol levels in the postmenopausal range
- Those patients that 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. Assessment of menopausal status should be confirmed prior to initiating adjuvant AI therapy.

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## Development and Revision History

This guideline was reviewed and endorsed by the Alberta Breast Tumour Team. Members include [surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a knowledge management specialist 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.

## Maintenance

A formal review of the guideline will be conducted in 2019. 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, adriamycin + cyclophosphamide; AI, aromatase inhibitor (anastrozole, letrozole or exemestane); C, cyclophosphamide; Cb, carboplatin; CMF, cyclophosphamide + methotrexate + 5-FU; D, docetaxel; DC, docetaxel + cyclophosphamide; DCbH, docetaxel + carboplatin + trastuzumab; ER, estrogen receptor; Dd, dose dense; FEC, 5-FU + epirubicin + cyclophosphamide; FEC-D, FEC x 3 □ D x3; FSH, follicle stimulating hormone; H, trastuzumab (Herceptin®); HER-2, human epidermal growth factor receptor 2; LHRH, luteinizing hormone–releasing hormone; LN, lymph node; P, paclitaxel; PR, progesterone receptor; TAC, docetaxel + adriamycin + cyclophosphamide

## 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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