

STUDY GUIDE

Guidance for Canadian Breast Cancer Practice: National Consensus Recommendations for the Systemic Treatment of Patients with HER2+ Breast Cancer in Both the Early and Metastatic Settings (2025 Update).

Research Excellence, Active Leadership Canadian Breast Cancer Alliance (REAL Alliance) [2] · 2026

Study Guide: Systemic Treatment for HR+/HER2- Metastatic Breast Cancer (2025 Consensus Recommendations)

This study guide provides a comprehensive overview of the national consensus recommendations for the management of Hormone Receptor-positive (HR+), Human Epidermal Growth Factor Receptor 2-negative (HER2-) metastatic breast cancer, as developed by the Research Excellence, Active Leadership (REAL) Canadian Breast Cancer Alliance.

Part 1: Key Concepts and Therapeutic Framework

1. Goals of Treatment

The primary goal of systemic treatment for metastatic HR+/HER2- breast cancer is to support patient well-being by:

- Stabilizing the disease and/or reducing cancer burden.
- Delaying disease progression.
- Improving quality of life.
- Prolonging overall survival (OS), acknowledging that metastatic disease is generally not curable.

2. Patient Categorization by Endocrine Sensitivity

Treatment selection is guided by a continuum of endocrine responsiveness rather than rigid classifications:

Category	Description
Endocrine-Sensitive	Patients who have not received prior/recent endocrine therapy (ET), such as de novo metastatic cases or recurrence >12 months after completing adjuvant ET.
Endocrine-Eligible	Patients whose cancer retains some responsiveness to ET despite relapse on or within 12 months of completing adjuvant ET, or progression on ET in the metastatic setting.
Endocrine-Ineligible	Patients with endocrine-refractory biology, typically due to extensive prior ET exposure with documented progression.

3. Precision Oncology and Biomarkers

Biopsy of recurrent lesions is strongly recommended to confirm diagnosis and reassess tumor biology (ER/PR/HER2 status). Routine testing for the following is essential:

- **Somatic Mutations:** *PIK3CA*, *PTEN*, *AKT*, and *ESR1*.
- **Germline Variants:** *BRCA1/2* mutations.
- **HER2 Status:** Identifying "HER2-low" (IHC 1+ or 2+/ISH-) or "HER2-ultralow" (IHC >0 but <1+) status to determine eligibility for antibody-drug conjugates (ADCs).

4. First-Line Standard of Care

For the majority of patients, the first-line (1L) standard is a combination of **Endocrine Therapy (ET) + a CDK4/6 inhibitor (CDK4/6i)**.

- **Preferred Agents:** Ribociclib or Abemaciclib.
- **Alternative:** Palbociclib (if others are contraindicated or not tolerated).
- **Hormonal Backbone:** Typically an Aromatase Inhibitor (AI).
- **Men and Pre/Perimenopausal Women:** Must receive Ovarian Function Suppression (OFS) or LHRH agonists alongside AIs to ensure efficacy.

5. Managing Targeted Therapy Side Effects

- **CDK4/6 inhibitors:** Require monitoring for neutropenia, hepatobiliary toxicity, and QTc prolongation (specifically for Ribociclib). Abemaciclib is notably associated with diarrhea.
- **PI3K/AKT/PTEN Inhibitors:** Frequently cause hyperglycemia, rash, and diarrhea. Inavolisib and Alpelisib require baseline and routine blood glucose monitoring.
- **Antibody-Drug Conjugates (ADCs):** Trastuzumab deruxtecan (T-DXd) carries a risk of Interstitial Lung Disease (ILD)/pneumonitis. Sacituzumab govitecan is associated with neutropenia and diarrhea.

Part 2: Short-Answer Practice Questions

Q1: What is the defining threshold for "HER2-ultralow" according to the 2025 guidelines?

Answer: HER2-ultralow is defined as membrane staining with an IHC score of >0 and <1+ in ≤10% of invasive cancer cells.

Q2: In which specific clinical scenario is the "triple therapy" of Inavolisib + Palbociclib +

Fulvestrant recommended? Answer: It is the standard of care for patients with *PIK3CA*-mutated HR+/HER2- breast cancer whose disease relapses on or within 12 months of completing adjuvant AI therapy.

Q3: What must be administered alongside an Aromatase Inhibitor (AI) in male patients or premenopausal women?

Answer: Pre/perimenopausal women must receive Ovarian Function Suppression (OFS) and men must receive a luteinizing hormone-releasing hormone (LHRH) agonist to ensure treatment efficacy.

Q4: How is "Visceral Crisis" defined, and how does it change the 1L treatment approach?

Answer: Visceral crisis is defined as severe organ dysfunction (e.g., rapidly increasing dyspnea at rest or bilirubin >1.5x ULN). In the *absence* of visceral crisis, CDK4/6i + ET is preferred; however, in a true crisis, chemotherapy (potentially a doublet) is prioritized for rapid response.

Q5: Why is Dihydropyrimidine Dehydrogenase (DPD) testing required before starting

Capecitabine? Answer: DPD deficiency can lead to severe, potentially fatal reactions to fluoropyrimidines. Patients with complete or near-complete deficiency should not receive capecitabine.

Q6: Which CDK4/6 inhibitor has demonstrated a statistically significant Overall Survival (OS) benefit in the 1L setting for premenopausal women (MONALEESA-7 trial)?

Answer: Ribociclib.

Part 3: Essay Prompts for Deeper Exploration

1. The Evolution of the Endocrine Backbone: From AIs to Oral SERDs. Discuss the clinical significance of *ESR1* mutations in metastatic breast cancer. Evaluate the data regarding oral Selective Estrogen Receptor Degraders (SERDs) like Elacestrant or Camizestrant compared to traditional therapies like Fulvestrant or Aromatase Inhibitors. How does the detection of *ESR1* mutations via ctDNA influence the timing of therapy changes?

2. Strategic Sequencing of Antibody-Drug Conjugates (ADCs). Compare and contrast the clinical data for Trastuzumab deruxtecan (T-DXd) and Sacituzumab govitecan. Address the challenges regarding the "ADC-after-ADC" sequence, including potential mechanisms of resistance related to the target antigen versus the cytotoxic payload.

3. Individualizing Care in Special Populations. Explain the REAL Alliance recommendations for treating elderly patients (≥75 years) and patients with CNS metastases. How do the goals of therapy

and the risk-benefit profiles of standard treatments (like CDK4/6 inhibitors) shift when treating these specific subgroups?

Part 4: Glossary of Important Terms

- **ADC (Antibody-Drug Conjugate):** A targeted therapy consisting of an antibody linked to a cytotoxic chemical (e.g., T-DXd, Sacituzumab govitecan).
- **AKT/PI3K/PTEN Pathway:** A signaling pathway often mutated in breast cancer (*PIK3CA*); targets include Inavolisib, Capivasertib, and Alpelisib.
- **CDK4/6 Inhibitor (CDK4/6i):** A class of drugs (Ribociclib, Abemaciclib, Palbociclib) that inhibits cell cycle progression; used as standard first-line treatment in combination with ET.
- **ctDNA (Circulating Tumor DNA):** Genetic material shed by tumors into the blood; used as a "liquid biopsy" to detect dynamic mutations like *ESR1*.
- **De Novo Metastatic:** Breast cancer that is already at the metastatic stage (Stage IV) at the time of initial diagnosis.
- **ESMO-MCBS:** The European Society for Medical Oncology Magnitude of Clinical Benefit Scale, used to grade the clinical value of new therapies.
- **ESR1 Mutation:** A mutation in the estrogen receptor gene that often emerges after treatment with Aromatase Inhibitors, leading to endocrine resistance.
- **LHRH Agonist:** A medication used to suppress the production of sex hormones (estrogen/testosterone), essential for treating HR+ cancer in men and premenopausal women.
- **PARP Inhibitor (PARPi):** A drug (e.g., Olaparib, Talazoparib) that targets the DNA repair pathway, specifically effective in patients with germline *BRCA1/2* mutations.
- **REAL Alliance:** Research Excellence, Active Leadership Canadian Breast Cancer Alliance; the expert committee responsible for these consensus recommendations.
- **SERD (Selective Estrogen Receptor Degradar):** A drug that binds to and degrades the estrogen receptor (e.g., Fulvestrant, Elacestrant).
- **SRE (Skeletal-Related Event):** Complications from bone metastases, such as fractures or pain; managed with bone-modifying agents like bisphosphonates or denosumab.