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Advances in Adjuvant Therapy for High-Risk Breast Cancer: A Canadian Clinical Approach

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Introduction

Breast cancer remains the second leading cause of cancer-related death among women in Canada.[1] In early-stage disease, the purpose of adjuvant therapies following surgical resection is to reduce the risk of recurrence. The advent of adjuvant endocrine therapy (ET) significantly reduced breast cancer recurrence and mortality; however, some patients have disease recurrence even 20 years after initial diagnosis.[2] Therefore, several advancements have been made to optimize cure rates and improve outcomes. As a heterogeneous disease, breast cancer outcomes are impacted by clinical, histological, and genomic features, which guide prognosis and selection of adjuvant therapy.[3-5] This review focuses on recent and emerging adjuvant therapies, specifically for high-risk patients across breast cancer subtypes: hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-positive (HER2-positive), and triple-negative breast cancer (TNBC).

HR-positive, HER2-negative Breast Cancer

The majority of patients with early-stage HR-positive, HER2-negative breast cancer are treated with upfront surgery followed by adjuvant ET. The duration of ET is typically five years for most patients, but some patients may benefit from extended therapy of up to 10 years.[2] Those with high-risk disease may require additional chemotherapy, cyclin-dependent kinase (CDK) 4/6 inhibitors, and/or poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors to reduce the risk of recurrence.

Many biomarker assays have been developed to guide decisions regarding adjuvant chemotherapy. The OncotypeDx 21-gene Recurrence Score (RS) is a 21-gene assay that is prognostic and has been validated to predict the benefit of adjuvant chemotherapy. The TAILORx trial demonstrated that patients with HR-positive, HER2-negative, T1 to T2, axillary node-negative disease did not benefit from the addition of adjuvant chemotherapy if the 21-gene RS was ≤25.[3] The RxPONDER trial investigated the assay in those with 1–3 lymph node-positive disease. In this trial, postmenopausal patients with a score of ≤25 did not benefit from adjuvant chemotherapy, whereas premenopausal patients did benefit from chemotherapy, regardless of the RS.[4] Recently, a novel prognostic tool, RSClin, has been developed utilizing data from the TAILORx trial to provide individual prognostic predictions regarding distant recurrence risk and the potential benefit of adjuvant chemotherapy.[6] These tools are routinely utilized in Canadian clinical practice to assist with patient-specific treatment decisions.

CDK4/6 inhibitors (e.g., palbociclib, ribociclib, abemaciclib) were initially approved in combination with ET for metastatic HR-positive, HER2-negative breast cancer. Recent trials have evaluated their efficacy as adjuvant therapy in early-stage disease. The NATALEE trial studied ribociclib combined with ET for three years in patients with Stage III or high-risk Stage II disease, and revealed a 25.1% reduced risk of recurrence at a median follow-up of 33.3 months [hazard ratio (HR): 0.749, 95% confidence interval (CI): 0.628-0.892; p =0.0012].[7,8] The monarchE trial investigated abemaciclib with ET for two years in node-positive patients and showed a 32.0% reduced risk of recurrence at 54 months (HR: 0.680, 95% CI: 0.599–0.772; p <0.001).[9] Neither trial demonstrated an overall survival (OS) benefit at the reported follow-up (ribociclib HR: 0.892, abemaciclib HR: 0.903), although longer-term data are awaited.[8,9] These trials highlight the benefits of adjuvant ribociclib or abemaciclib in patients

CDK4/6 Inhibitor (*Trial*)	Abemaciclib (*monarchE trial*)	Ribociclib (*NATALEE trial*)
Treatment	2 years abemaciclib + ET	3 years ribociclib + ET (anastrozole or letrozole)
Histology	HR-positive, HER2-negative	HR-positive, HER2-negative
Menopausal Status	Premenopausal or postmenopausal	Premenopausal or postmenopausal
Disease Eligibility	≥4 positive ALN ***Or*** 1–3 positive ALN and: • Tumour ≥5 cm or • Grade 3 tumour or • Ki-67 ≥20%	Stage III or IIB disease ***Or*** Stage IIA with ≥1 positive ALN ***Or*** Stage IIA with 0 ALN and: • Grade 3 tumour or Grade 2 tumour with Ki-67 ≥20% or high-risk genomic features[a]
Adverse Events (any grade)	Diarrhea (83.5%), neutropenia (45.8%), anemia (24.4%), elevated liver transaminases (15.5%)	Neutropenia (62.5%), elevated ALT (19.5%), elevated AST (16.9%), QT prolongation (5.3%)
iDFS HR (95% CI)	0.680 (0.599–0.772)[b]	0.749 (0.628–0.892)[c]
dRFS HR (95% CI)	0.675 (0.588–0.774)[b]	-
dDFS HR (95% CI)	-	0.749 (0.623–0.900)[c]
OS HR (95% CI)	0.903 (0.749–1.088)[b]	0.892 (0.661–1.203)[c]

Table 1. Eligibility and efficacy of adjuvant treatment with abemaciclib or ribociclib; *courtesy of Samitha Andrahennadi, MD and Mita Manna, MD, FRCPC.*

[a] OncotypeDx recurrence score (RS) ≥26; or high-risk score by Prosigna PAM50, MammaPrint, or EndoPredict
[b] At 54 months of median follow-up
[c] At 33 months of median follow-up

Abbreviations: ALN: axillary lymph nodes, **ALT:** alanine transaminase, **AST:** aspartate transaminase; **CDK:** cyclin-dependent kinase; **CI:** confidence interval; **dDFS:** distant disease-free survival; **dRFS:** distant relapse-free survival; **ET:** endocrine therapy; **HR:** hazard ratio; **iDFS:** invasive disease-free survival; **OS:** overall survival

with high-risk HR-positive, HER2-negative breast cancer. Conversely, the PALLAS and Penelope-B trials showed no benefit of palbociclib, which is therefore not utilized in the adjuvant setting.[10,11] **Table 1** details adjuvant CDK4/6 inhibitor trial eligibility and results.[7–9,12]

The OlympiA trial studied one year of adjuvant treatment with the PARP inhibitor olaparib in patients with early-stage breast cancer with germline BReast CAncer (BRCA) mutations. Among participants, 18% had HR-positive, HER2-negative breast cancer.[13] Eligibility included residual disease post neoadjuvant chemotherapy with a clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG) score of ≥3, or ≥4 positive lymph nodes post-surgery.[13] At 6.1 years of follow-up, olaparib improved the 6-year invasive disease-free survival (iDFS) (79.6% vs. 70.3%; HR: 0.65, 95% CI: 0.53–0.78) and OS (87.5% vs. 83.2%; HR: 0.72, 95% CI: 0.56–0.93).[14] Adjuvant olaparib is a well-tolerated option for high-risk patients with germline BRCA mutations. The National Comprehensive Cancer Network recommends hereditary cancer testing for patients with specific risk factors such as breast cancer at ≤50 years or triple-negative disease at ≤60 years of age.[15] In Canada, BRCA testing criteria vary by province.

Several Phase III studies are underway investigating the efficacy of oral selective estrogen receptor degraders (SERDs) versus standard adjuvant ET, or as extended therapy after standard adjuvant ET. These include giredestrant (lidERA Breast Cancer, NCT04961996), imlunestrant (EMBER-4, NCT05514054), camizestrant

(CAMBRIA-2, NCT05952557), and elacestrant (ELEGANT, NCT06492616).

HER2-positive Breast Cancer

The standard treatment for patients with HER2-positive disease combines systemic chemotherapy with HER2-directed therapy. Efforts continue to optimize therapies to achieve a pathologic complete response (pCR) and reduce recurrence in patients with residual disease.

The KATHERINE trial demonstrated that trastuzumab emtansine (T-DM1) significantly improves iDFS and OS in patients with residual disease following neoadjuvant therapy (7-year iDFS: 80.8% vs. 67.1%; HR: 0.54, 95% CI: 0.44–0.66; p <0.0001; 7-year OS: 89.1% vs. 84.4%; HR: 0.66, 95% CI: 0.51-0.87; p =0.003).[16] The APHINTY trial included patients without prior neoadjuvant therapy, and showed that adding pertuzumab to adjuvant trastuzumab and chemotherapy improved 8-year iDFS in node-positive patients (86.1% vs. 81.2%; HR: 0.72, CI: 0.60–0.87).[17] These results show a potential benefit of dual anti-HER2 therapy in node-positive patients, though long-term OS data are needed. It remains unknown whether patients achieving pCR still require adjuvant dual anti-HER2 therapy.

The ExteNET trial showed that adding neratinib, a tyrosine kinase inhibitor, for one year after trastuzumab improved iDFS, particularly in HR-positive patients (5-year iDFS: 90.8% vs. 85.7%; HR: 0.58, 95% CI: 0.41–0.82; p =0.002).[18] In HR-positive patients with residual disease post-neoadjuvant therapy, an 8-year OS benefit was observed (91.3% vs. 82.2%; HR: 0.47, 95% CI: 0.23–0.92; p =0.031).[18] However, these results preceded the routine use of T-DMI and dual anti-HER2 therapy, and the role of extended neratinib in this context remains unclear.

Patients with residual disease following neoadjuvant therapy are at a high risk for recurrence, prompting ongoing studies. The CompassHER2RD trial (NCT04457596) is evaluating the addition of tucatinib, an oral HER2-specific tyrosine kinase inhibitor, to T-DM1, based on its benefit in metastatic breast cancer.[19] Similarly, the DESTINY-Breast05 trial (NCT04622319) is comparing the antibody-drug conjugate (ADC) trastuzumab deruxtecan to T-DM1, given its significant progression-free survival (PFS) improvement in the metastatic setting.[20] Advancements are being made to identify high-risk patients and personalize clinical decision-making for patients with HER2-positive disease. These include the HER2DX risk score and the HER2DX pCR score, which use genetic signatures and tumour pathology to predict prognosis and likelihood of achieving pCR after neoadjuvant therapy.[5] Although not routinely utilized in clinical practice, these scores could be used to stratify patients into high- or low-risk for the purpose of escalation or de-escalation of treatment.

TNBC

TNBC is characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression, and is associated with aggressive biology, higher recurrence risk, and poorer OS. Historically, systemic chemotherapy was the standard treatment due to the limitations of targeted therapy. The introduction of immunotherapy in metastatic TNBC showed promising antitumour activity, leading to the pivotal KEYNOTE-522 trial.[21] This trial demonstrated improved pCR rates with pembrolizumab, an immune checkpoint inhibitor, plus neoadjuvant chemotherapy in early-stage TNBC (64.8% vs. 51.2%; p <0.001), regardless of programmed cell death ligand 1 (PD-L1) status.[21] Recently, data has also shown improved OS at 60 months (86.6% vs. 81.7%; p =0.002).[22] The benefit of continuing adjuvant pembrolizumab in patients achieving pCR remains unclear and is being investigated in the ongoing Phase III optimICE-PCR trial (NCT05812807).

Patients with residual disease may benefit from adjuvant capecitabine, as the CREATE-X trial showed improved 5-year iDFS in the TNBC cohort receiving capecitabine (69.8% vs. 56.1%; HR: 0.58, 95% CI: 0.39–0.87).[23] Future studies are needed to evaluate the safety and efficacy of combining adjuvant capecitabine with pembrolizumab, as high-risk patients may benefit from this approach to further reduce their risk of recurrence. In addition, the OlympiA trial demonstrated that one year of olaparib significantly improved OS and iDFS.[13] Among participants, 82% had TNBC and were eligible if they had residual disease after neoadjuvant therapy or ≥T2 or node-positive disease in the adjuvant setting (see HR-positive section).[13] As such, one year of adjuvant olaparib is indicated in this group of patients with TNBC and germline BRCA mutations. However, the benefit of olaparib in addition to pembrolizumab and/or capecitabine remains uncertain.

Sacituzumab govitecan (SG) was the first approved ADC for metastatic TNBC, as it demonstrated improved PFS and OS compared to single-agent chemotherapy in heavily pre-treated patients.[24] The Phase III SASCIA trial (NCT04595565) will investigate the efficacy of SG in patients with HER2-negative breast cancer who have residual disease following neoadjuvant chemotherapy. Similarly, the ASCENT-05/OptimICE-RD trial (NCT05633654) will compare adjuvant SG plus pembrolizumab versus pembrolizumab plus capecitabine versus pembrolizumab alone in patients with TNBC and residual invasive disease after neoadjuvant chemotherapy.

Future Directions

A new area of research that uses circulating tumour DNA (ctDNA) for surveillance and monitoring of disease progression and therapy response is emerging. The rationale is that detections in serum ctDNA may reflect early disease recurrence in the absence of clinical or imaging findings of metastasis, which is referred to as minimal residual disease (MRD).[25] A prospective study identified metastatic recurrence using ctDNA at a median lead time of 12.4 months.[25] As such, patients in which surveillance ctDNA identifies MRD may be candidates for escalated treatment to reduce the risk of developing clinical metastasis; however, there is a need for studies demonstrating the clinical benefit of this approach. The c-TRAK TN trial was a Phase II trial investigating ctDNA surveillance and intervention in 161 patients with high-risk TNBC with trackable mutations.[26] The trial intention was to treat MRD with pembrolizumab; however, the initial surveillance ctDNA after adjuvant therapy identified a high rate of MRD at 72%.[26] Only five patients commenced pembrolizumab, and they did not sustain clearance of ctDNA.[26] The TREAT ctDNA trial (NCT05512364) is a Phase III trial that will investigate the benefit of escalating adjuvant ET to elacestrant in patients with a positive ctDNA, suggesting MRD; and the DARE trial (NCT04567420) is a Phase II trial that will investigate escalating treatment to palbociclib and fulvestrant in this setting.

Summary

The last decade has brought remarkable innovation in adjuvant therapy options for high-risk breast cancer, including CDK4/6 inhibitors, PARP inhibitors, HER2-directed therapies, and immunotherapy. Escalated adjuvant therapy continues to benefit high-risk patients while sparing low-risk patients from unnecessary treatment. Efforts to better stratify and identify high-risk patients are ongoing, which includes stratification for the use of ADCs and oral SERDs. Additionally, the use of ctDNA for surveillance to identify patients at risk of early recurrence is an emerging approach, with ongoing research to support a clinical benefit. These advancements highlight a future focused on precision in tailoring adjuvant therapies for improved outcomes.

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