Canadian Oncology Today

Volume 2, Issue 1

ISSN 2818-1131 (print)
ISSN 2818-114X (online)

Spring 2025

Editorial Board

Normand Blais, MD, FRCPC

Co-Founder, Groupe d'Études en Oncologie du Québec
Chair, Thoracic Oncology Program, CHUM Cancer Center

Christine Brezden-Masley, MD, PhD, FRCPC

Medical Oncologist & Medical Director, Cancer Program,
Sinai Health System
Director, Marvelle Koffler Breast Centre at Sinai Health
Founder, COMET Clinical Trials Consortium

Sharlene Gill, MD, MPH, MBA, FACP, FRCP(C)

Professor of Medicine, University of British Columbia
Chair, Canadian Clinical Trials Group (CCTG) GI Disease
Site Committee
Chair, BC Cancer Medical Advisory Committee President, Canadian
Association of Medical Oncologists

Sébastien J. Hotte, MD, MSc (HRM), FRCPC

Medical Oncologist, Juravinski Cancer Centre, Hamilton
Associate Professor, Clinical and Academic Head, Division of Medical
Oncology, Department of Oncology, McMaster University
Chair, Canadian Clinical Trials Group (CCTG) GU Disease
Site Committee

Table of Contents

Canadian Oncology Today is published 3 times per year in English and French.

To contribute to a future issue, email us at info@catalytichealth.com. Submission guidelines and editorial policies are available on the journal website, **canadianoncologytoday.com**.

To subscribe to Canadian Oncology Today and more open access scientific specialty journals published by Catalytic Health, please visit **catalytichealth.com/cot**.

The content of this journal qualifies for Section 2 (self-learning) CPD credits under the Royal College's Maintenance of Certification (MOC) program. For more information on how journal articles can meet your CPD needs, please consult the Royal College's website. For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

For your mNSCLC patient with PD-L1 expression <1%

(predefined subgroup in open-label CheckMate 9LA trial)

Consider the option of PrOPDIVO® + PrYERVOY®

+ 2 cycles of platinum-doublet chemotherapy

OPDIVO (nivolumab), in combination with YERVOY (ipilimumab) and 2 cycles of platinum-doublet chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no EGFR or ALK genomic tumour aberrations, and no prior systemic therapy for metastatic NSCLC.[1,2]

PrOPDIVO® (nivolumab) + PrYERVOY® (ipilimumab) + 2 cycles of platinum-doublet chemotherapy

Demonstrated improved OS vs. platinum-doublet chemotherapy alone, irrespective of PD-L1 expression, in a predefined subgroup analysis in CheckMate 9LA[1,3]*

- In all randomized patients, OS events for OPDIVO + YERVOY + platinum-doublet chemotherapy were 156/361 vs. 195/358 for platinum-doublet alone (HR 0.69 [96.71% CI: 0.55, 0.87]); p=0.0006†; median OS was 14.1 months vs. 10.7 months
- In the subgroup of PD-L1 <1 patients, OS events for OPDIVO + YERVOY + platinum-doublet chemotherapy were 69/135 vs. 89/129 for platinum-doublet alone (HR 0.62‡ [95% CI: 0.45, 0.85]); median OS was 16.8 months vs. 9.8 months
- In the subgroup of PD-L1 ≥1 patients, OS events for OPDIVO + YERVOY + platinum-doublet chemotherapy were 105/203 vs. 139/204 for platinum-doublet alone (HR 0.64‡ [95% CI: 0.50, 0.82]); median OS was 15.8 months vs. 10.9 months

OPDIVO Safety Information[1]

Clinical use:

Efficacy and safety not established in pediatric patients.

Most serious warnings and precautions:

Severe/fatal immune-mediated adverse reactions (imARs): OPDIVO as monotherapy or in combination with YERVOY (ipilimumab) can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and autoimmune hemolytic anemia. Immune-mediated adverse reactions may involve any organ system. Onset may occur during treatment or months after the last dose. Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Monitor patients for signs and symptoms of imARs and appropriately manage with treatment modifications. Permanently discontinue for any severe imARs that recur and for any life-threatening imARs.

Administration: Administer OPDIVO under the supervision of physicians experienced in the treatment of cancer.

Allogeneic hematopoietic stem cell transplantation (HSCT): Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host disease (GVHD) and transplant-related mortality. Complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grades 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic venoocclusive disease (VOD), and other immune-mediated adverse reactions, and intervene promptly.

Multiple myeloma: Increased mortality in patients with multiple myeloma [not an approved indication] when OPDIVO is added to a thalidomide analogue and dexamethasone. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when OPDIVO was administered in combination with YERVOY vs. OPDIVO alone
- Severe cases of these imARs have been observed, including fatal cases. Monitor patients for signs and symptoms of:
  - Cardiac adverse events and pulmonary embolism with combination therapy
  - Endocrinopathies, including hypothyroidism, hyperthyroidism, hypoparathyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis
  - Diarrhea, additional symptoms of colitis, and cytomegalovirus (CMV) infection/reactivation
  - Hepatotoxicity, including hepatitis
  - Pneumonitis or interstitial lung disease
  - Nephrotoxicity, including nephritis and renal failure
  - Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Encephalitis
  - Aplastic anemia
  - Myelitis (including transverse myelitis)
  - Autoimmune hemolytic anemia
  - Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
  - Other imARs, including solid organ transplant rejection and rapid-onset and severe graft-versus-host disease (GVHD)
- Infusion reaction
- Patients on controlled sodium diet
- Caution when driving or operating a vehicle or potentially dangerous machinery
- Haemophagocytic lymphohistiocytosis (HLH)
- Effective contraception in women of reproductive potential
- Pregnancy and nursing women
- Has not been studied in patients with moderate or severe hepatic or severe renal impairment

For more information:

Please consult the OPDIVO Product Monograph at www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf for important information relating to adverse reactions, drug interactions, and dosing, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

YERVOY Safety Information[2]

Clinical use:

Efficacy and safety not established in pediatric patients.

Contraindication:

In patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life threatening.

Most serious warnings and precautions:

Severe/fatal immune-mediated adverse reactions (imARs): YERVOY as monotherapy or in combination with OPDIVO (nivolumab) can cause severe/fatal imARs, including enterocolitis, intestinal perforation, hepatitis, dermatitis (incl. toxic epidermal necrolysis), Stevens-Johnson syndrome, neuropathy, endocrinopathy, pneumonitis, interstitial lung disease, myocarditis, encephalitis, myasthenia gravis, autoimmune hemolytic anemia and other organ system toxicities. Most occurred during the induction period; onset months after the last dose has been reported. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Monitor patients for signs and symptoms suggestive of imARs. Permanently discontinue treatment for any severe imAR reaction that recurs and for any life-threatening imAR.

Consult the OPDIVO (nivolumab) Product Monograph prior to initiation of YERVOY in combination with OPDIVO.

Administration: Administer YERVOY under the supervision of physicians experienced in the treatment of cancer.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when YERVOY was administered in combination with OPDIVO vs. YERVOY alone
- Patients who have had a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy
- Severe cases of these imARs have been observed, including fatal cases. Monitor for signs/symptoms of:
  - Gastrointestinal adverse reactions
  - Hepatic adverse reactions
  - Pulmonary adverse reactions
  - Renal adverse reactions
  - Skin adverse reactions
  - Encephalitis
  - Neuropathies
  - Endocrinopathies, including diabetes mellitus (including fulminant type 1 diabetes), and diabetic ketoacidosis
- Other imARs including ocular events
- Haemophagocytic lymphohistiocytosis (HLH)
- Vogt-Koyanagi-Harada syndrome
- Serous retinal detachment
- Graft-versus-host disease (GVHD)
- Solid organ transplant rejection in the post-marketing setting
- Infusion reaction
- Patients on immunosuppressive therapy for life-threatening disease or condition
- Autoimmune hemolytic anemia
- Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
- Patients on controlled sodium diet
- Concurrent administration with vemurafenib
- Caution when driving or operating machinery
- Patient counselling information: imARs and fatigue
- Not studied in patients with hepatic impairment
- Not studied in patients with renal impairment
- Pregnancy and nursing women
- Effective contraception in women of reproductive potential
- Close monitoring required: liver function tests, thyroid function test, electrolytes, any signs of imARs

For more information:

Please consult the YERVOY Product Monograph at www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf for important information relating to adverse reactions, management of imARs, drug interactions, and dosing information, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

CI: confidence interval; HR: hazard ratio; mNSCLC: metastatic non-small-cell lung cancer; OS: overall survival; PD-L1: programmed death-ligand 1.

* CheckMate 9LA: a randomized, multicenter, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK tumour aberrations. Patients (N=719) were randomized (1:1) to OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks in combination with YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

† Stratified log-rank *p*-value.

‡ Unstratified hazard ratio.

References: 1. OPDIVO Product Monograph. Bristol-Myers Squibb Canada. **2.** YERVOY Product Monograph. Bristol-Myers Squibb Canada. **3.** Paz-Ares L, Ciuleanu T-E, Cobo M, *et al*. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy in patient with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncology*. 2021;22:198-211.

Bristol Myers Squibb®

About the Authors

Mairi Lucas, MD

Dr. Mairi Lucas completed her medical oncology fellowship in Breast Medical Oncology at BC Cancer Vancouver and is a Medical Oncologist treating breast and gynecological malignancies at BC Cancer, Surrey and UBC Assistant Clinical Professor.

Affiliations: Dept. Medical Oncology, BC Cancer, Vancouver, British Columbia, Canada

Stephen K. L. Chia, MD, FRCPC

Dr. Chia is a Full Professor in the Division of Medical Oncology, Head of the Division of Medical Oncology, UBC and a staff medical oncologist with the BC Cancer, Vancouver Cancer Centre. He has a full-time clinical practice focusing on breast cancer and in new drug development. He is the Chair of the BC Cancer Breast Tumour Group and Head of the Department of Clinical Research. He is also the Co-Chair of the Breast Disease Site for Canadian Cancer Trials Group (CCTG) and a member of the NCI Breast Steering Committee. Dr. Chia is recognized both nationally and internationally for his research work on breast cancer. His focus is on clinical trials and translational research. He has published over 185 peer-reviewed papers. He was past subject editor for British Journal of Cancer. He is the current author for UpToDate for Prognostic and Predictive Factors in Metastatic Breast Cancer. He holds numerous peer reviewed grants and currently holds a Michael Smith Research HPI award.

Affiliations: Dept. Medical Oncology, BC Cancer, Vancouver, British Columbia, Canada

doi.org/10.58931/cot.2025.2130

The Role of ctDNA in Breast Cancer: Prognosis and Clinical Utility

Mairi Lucas, MD
Stephen K. L. Chia, MD, FRCPC

Introduction

Breast cancer remains the most common cancer among women globally, with significant morbidity and mortality.[1] Current treatment for breast cancer, both in the early stage and metastatic setting, is based on a tumour biopsy and immunohistochemical detection of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) expression.[1] Though substantial research has been undertaken over the years to establish new prognostic and predictive biomarkers in breast cancer, most have not demonstrated significant clinical utility. Circulating tumour DNA (ctDNA) is increasingly used across various cancer types for precision medicine. In this article, we discuss the current roles of ctDNA in breast cancer prognosis and its clinical utility in treatment decision-making in early- and advanced-stage settings.

Technical Aspects

Cancer cells can shed DNA fragments into the circulation through the cellular breakdown of tumour cells via apoptosis and necrosis.[2] Circulating tumour DNA (ctDNA) comprises short fragments of DNA that can be detected and analyzed in the blood, providing a potentially minimally invasive approach for disease monitoring and evaluating response to therapy.[2]

Several approaches can be used for ctDNA detection. Tumour-agnostic approaches involve testing broadly for multiple mutations with a predetermined panel of genes, while tumour-informed assays are individualized tests based on mutations/alterations observed in the individual's tumour.[2]

Historically, for tumour-agnostic approaches, the same ctDNA assay would be used for each patient with breast cancer without needing prior knowledge of the primary tumour's mutations.[2] By testing for multiple mutations, this approach allows for the discovery of *de novo*/acquired genomic alterations that might correlate with treatment resistance and potentially serve as treatment targets. Therefore, this approach may play a more important role in the metastatic setting to detect emergent or truncal mutations that have developed over time.[2] However, this technique usually requires a higher tumoral fraction of total cell-free DNA and, therefore, can have a lower sensitivity.[2] Another consideration with some tumour-agnostic approaches is the potential false positive results due to clonal hematopoiesis of indeterminate potential (CHIP). Mutations in hematopoietic progenitor cells occur as part of aging, and these CHIPs can be mistaken for tumour mutations. Additional white blood cells/buffy coat testing can help account for and correct for these CHIP mutations.[2]

With tumour-informed assays, the patient's tumour is sequenced (either whole exome sequencing [WES] or whole genome sequencing [WGS]) and an individualized ctDNA assay of a range of variants is created. This extra step of sequencing and developing a unique assay can make this approach more time-consuming than tumour-agnostic approaches. However, tumour-informed assays are often more sensitive at detecting molecular recurrence of disease, though they may miss emergent mutations over time.[2] These characteristics make these approaches more valuable in the early-stage setting to detect early recurrences.[2]

The amount of ctDNA in the total blood is usually low; therefore, different techniques are used to amplify this signal, which contributes to the sensitivity of the assay (**Table 1**).[2,3]

ctDNA in Early Breast Cancer

Prognostic Value of ctDNA

Current surveillance in patients with early-stage breast cancer involves clinical history,

Technique	Description
Amplicon-based	In amplicon-based NGS, gene-specific amplicons are used to amplify certain genomic regions expected to harbour tumour-derived mutations prior to NGS. This is often combined with unique molecular barcodes to reduce errors. Can be used in both tumour-agnostic assays or personalized tumor-informed assays.[2,3] This technique can usually be performed with a simple workflow allowing for a high throughput. This may be at the cost of lower sensitivity for low-frequency mutations compared to ddPCR; however, the sensitivity is assay-dependent.
Hybridization capture	Specific DNA regions are captured by hybridization using targeted probes. Non-target molecules are washed away, meaning the remaining library is enriched for the regions of interest. Can be used in both tumour-agnostic assays or personalized tumor-informed assays.[2,3] This can be more sensitive than amplicon-based NGS; however, it often requires a more expensive and complex workflow.
Methylation analysis	Methylation patterns are specific to cell types. By using techniques such as bisulfite conversion, cancer-specific methylation patterns can be captured and amplified.[2,3]
ddPCR	The DNA sample is partitioned into multiple droplets, in which isolated PCR occurs. Analyzing each droplet individually increases the sensitivity and reproducibility.[2,3]
BEAMing	Magnetic beads with primers designed to target the regions of interest are emulsified into droplets, similar to ddPCR, allowing PCR amplification within the individual droplets.[2,3]

Table 1. Different techniques used in ctDNA assay; *courtesy of Mairi Lucas, MD and Stephen Chia, MD.*

Abbreviations: BEAM: beads, emulsion, amplification, and magnetics, **ctDNA:** circulating tumour DNA, **dd:** droplet digital, **NGS:** next-generation sequencing, **PCR:** polymerase chain reaction

breast examination, annual breast imaging, and further imaging based on symptoms. Historical trials did not demonstrate an improvement in overall survival (OS) when more intensive imaging surveillance was used which aimed to provide earlier detection of metastatic disease.[1] There is increasing interest in the use of ctDNA due to its sensitivity and specificity to monitor for recurrences in patients with early-stage breast cancer, and thus, potentially to act at an earlier time point.[4]

In one of the earlier and larger studies evaluating ctDNA for this purpose, Garcia-Murillas et al. used personalized tumour-informed digital PCR (dPCR) assays to test for ctDNA at predetermined time points in 101 patients with breast cancer who had received definitive surgery with no clinical evidence of metastatic disease.[4] Across breast cancer subtypes, ctDNA detection was associated with relapsed disease (hazard ratio [HR], 25.2; 95% confidence interval [CI], 6.7–95.6; p-value: <0.001) with a median lead time of 10.7 months before radiologically confirmed metastatic disease.[4] While patients who remained ctDNA-negative were less likely to relapse, 6 (21.6%) patients with ctDNA-negative results experienced a relapse, with 3 of these being with brain-only relapses.[4] The blood-brain barrier has long been postulated as the reason that the brain is a sanctuary site for metastatic disease, and also may result in less detectable ctDNA in patients with metastatic disease in the brain only.[4]

Further studies have shown that ctDNA is a prognostic factor across breast cancer subtypes and can detect relapse earlier than conventional imaging.[5,6] In a study by Coombes et al., 49 patients with early-stage breast cancer were monitored with ctDNA testing using a tumour-informed assay. Of the patients who relapsed, 89% (16/17) had detectable ctDNA, with ctDNA detection occurring a median of 8.9 months prior to clinical relapse.[5] It is noteworthy, though, that in studies in which ctDNA is analyzed and detected in real-time, the triggered imaging

studies often detect evidence of metastatic disease already at that time point.

Neoadjuvant treatment for breast cancer is now recommended in HER2+ breast cancer that is >2 cm or node-positive, as well as in triple-negative breast cancer (TNBC) with clinical T2 disease or greater.[1] Multiple trials have shown the prognostic implications of gaining a pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) in these subtypes.[1] For those who do not achieve a pCR, adjuvant therapy can be escalated to reduce the risk of breast cancer recurrence.[1] In 196 patients with early-stage TNBC, who had residual disease post-NAC, the detection of ctDNA post was associated with a significantly worse distant disease-free survival (DDFS) (median, 32.5 months vs. not reached; HR, 2.99; 95% CI, 1.38–6.48; p-value: 0.006) and OS compared to those who remained ctDNA-negative.[6]

In an exploratory analysis of the I-SPY2 trial, in which tumour-informed ctDNA testing was performed pre-NAC, during treatment, and prior to surgery in high-risk early breast cancer patients.[7] Patients who did not achieve a pCR but were ctDNA-negative post-NAC had a similar rate of recurrence as patients with a pCR, suggesting ctDNA may be more informative regarding prognosis than pCR.[7] This was also reflected in a study that showed that the detection of ctDNA can further delineate those who are most at risk of recurrence within the residual cancer burden (RCB) score categories in TNBC. ctDNA-positivity was associated with inferior 3-year OS (50% vs. 86%, p-value: 0.002) compared with ctDNA-negative disease in those with RCB II disease, with a trend towards worse outcomes in those with ctDNA-positive/RCB III disease.[8]

Clinical Utility in Early Stage

As the above studies have highlighted, ctDNA can be prognostic; however, what remains unclear and not adequately tested as the primary objective in large randomized clinical trials, is whether this information changes clinical practice and, more importantly, whether it significantly alters patient outcomes.

The MonarchE trial assessed the use of abemaciclib in patients with high-risk, ER-positive, HER2-negative disease. In this study, a cohort of patients was identified with sufficient primary tumour tissue available to perform WES and subsequently create a personalized tumour-informed assay (Signatera™ ctDNA assay – Natera Inc.) to assess the utility of ctDNA within this study.[9] Of the 910 patients reviewed, 8% were ctDNA-positive at baseline.[9] Of that group, 59% remained persistently ctDNA-positive on treatment with adjuvant abemaciclib, while the remaining 41% became ctDNA-negative (undetectable).[10] Patients who were ctDNA-positive at baseline had a worse invasive disease-free survival (IDFS) of 20% (95% CI, 12.5–82.0) at 4 years compared to 79.1% (95% CI, 76.4–82) in the baseline ctDNA-negative group (p-value: <0.001).[10] Importantly, rates of IDFS events varied between those who were persistently ctDNA-positive and those who became ctDNA-negative, with 100% and 42% having events, respectively.[10] The prognostic value of ctDNA was also observed within the persistently ctDNA-negative group, with only 14% having an IDFS event compared to 93% in the group who became ctDNA-positive over time.[10] The majority of the events in ctDNA-positive patients were distant relapses.[10] This further highlights the prognostic ability of ctDNA, but also suggests that abemaciclib may allow some patients to clear ctDNA and reduce their risk of cancer recurrence. The lead time between the ctDNA detection and IDFS events varied, but was relatively short at 7 months (range 0–48) in those originally ctDNA-negative that became ctDNA-positive. It remains unknown whether instituting or changing treatment at the point of ctDNA detection without clinical evidence of metastatic disease affects outcomes.[10]

The ongoing DARE trial enrolled and followed patients with high-risk ER-positive disease on adjuvant endocrine therapy with serial ctDNA screening every 6 months using a tumour-informed assay (Signatera™ ctDNA assay – Natera Inc.).[11] This study randomized patients who become ctDNA-positive to continue current therapy versus changing to palbociclib and fulvestrant.[11] The ctDNA positivity rate in the first test was 3.8%, and the anytime ctDNA detection rate among those with serial testing was 7.2%.[11] An interim analysis showed that 5 (16.7%) patients with ctDNA-positive disease also had asymptomatic disease on imaging.[11] It remains unknown what the optimal time interval for ctDNA testing is, and whether this varies between breast cancer subtypes. Outcomes for disease-free survival are awaited and will hopefully shed more light on the clinical utility of ctDNA in breast cancer in terms of treatment of ctDNA-positive disease in the absence of radiological evidence of metastatic

disease. Most importantly, the endpoint of these types of intervention studies should be OS, to overcome the issue of lead time bias.

The c-TRAK TN trial was a multicentre Phase II trial that integrated prospective ctDNA monitoring with a tumour-informed assay (Thermo Fisher Custom TaqMan Assay Design Tool) every 3 months up to 1 year post-completion of adjuvant therapy in patients with early-stage TNBC.[12] Patients who became ctDNA-positive and staging imaging-negative were randomized to observation or intervention with pembrolizumab.[12] Within 12 months, 27.3% of patients became ctDNA-positive; however, of the patients randomized to the intervention arm, 72% had metastatic disease on imaging at the time of ctDNA detection.[12] This again highlights two important questions regarding ctDNA testing in early breast cancer: firstly, regarding the sensitivity of the assay, and secondly, regarding the need for clarity on the optimal interval for testing.

Lastly, the ZEST trial was a Phase III trial assessing niraparib in patients with BRCA-mutant, ER-positive, HER2-negative breast cancer or TNBC, post-completion of definite therapy with detectable ctDNA and no radiological evidence of disease.[13] The ZEST trial was closed early due to a low randomization rate as only 8% of patients screened were ctDNA-positive, and 49% of these patients had radiological evidence of recurrence at the time of the positive ctDNA test.[14] These 40 patients were randomized to either placebo or niraparib, and the niraparib arm had a numerical longer recurrence-free interval. However, given the small number of patients, this trial was not powered to evaluate the efficacy of niraparib.[14]

Further studies are in progress assessing the clinical utility of ctDNA for early-stage breast cancer.

ctDNA in Metastatic Breast Cancer (MBC)

Prognostic Aspects of ctDNA in Metastatic Breast Cancer

In contrast to early-stage breast cancer, which is focused on the early detection of ctDNA or molecular recurrence in the absence of overt evidence of metastatic disease on imaging, ctDNA is detectable in the majority of patients with known MBC.[15]

Similar to the early-stage setting, an increase in the ctDNA tumour fraction in the metastatic setting is associated with worse outcomes.[15,16] In the LOTUS trial that assessed the oral AKT inhibitor ipatasertib with paclitaxel in first-line metastatic TNBC, a high ctDNA fraction was associated with worse progression-free survival regardless of the treatment arm.[17] A systematic review and meta-analysis by Dickinson et al. reviewed 75 studies that analyzed ctDNA data and survival outcomes in patients with MBC.[16] In this meta-analysis, the detection of specific ctDNA alterations was significantly associated with reduced survival (HR, 1.40; 95% CI, 1.22–1.58; p-value: <0.001), and this association was consistent across breast cancer subtypes (hormone receptor-positive, HER2-positive, and TNBC).[16]

Clinical Utility in MBC

Previous studies showed that detection of circulating tumour cells (CTCs) correlates with a higher risk of recurrence.[18] However, studies that adjusted treatment in the metastatic setting based on CTC did not improve outcomes.[18] Therefore, while the prognostic value of rising ctDNA in metastatic disease has been shown,[16,17] it remains unclear if changing treatment based on this instead of conventional imaging progression will lead to an improved OS. The clinical utility of ctDNA detection in MBC currently relates to its ability to detect specific mutations in tumour cells that match targeted therapies.

The mutational landscape in MBC is not static and changes over time with the emergence of different sub-clones. Repeat tumour biopsies of progressive metastatic sites can help identify new mutations and guide treatment options. However, a biopsy may not represent all malignant cells due to heterogeneity within metastatic sites.[19] ctDNA testing may provide more detailed information about the disease's mutational landscape and clonality based on variant allele frequency of the various genomic alterations shed.[19]

The LOTUS trial showed 100% concordance between ctDNA and tissue sequencing in patients with *PIK3CA* or *AKT1* mutations, suggesting the ctDNA may be an excellent non-invasive test to assess these mutations rather than undergoing further tissue biopsies, particularly for these specific mutations with available targeted treatments.[17]

The plasmaMATCH trial was an open-label, multicohort trial assessing the accuracy of ctDNA testing in advanced breast cancer, and the ability of ctDNA testing to select patients for targeted therapy based on the ctDNA

alterations detected.[20] Tests for ctDNA were done via two different technologies, dPCR and targeted sequencing with a 73 gene panel (Guardant360-Guardant Health). Where feasible, this was also compared to results from a tissue biopsy.[20] There was 96–99% agreement in identifying mutations between ctDNA dPCR and targeted sequencing.[20] However, it should be noted that there was greater discordance for ctDNA results regarding mutations with low allele frequency, which may reflect the sensitivity of the assay.[20] When dPCR ctDNA results were compared to tissue sequencing from contemporaneous and time-discordant biopsies, the sensitivity of ctDNA was 98% and 85%, respectively.[20] Mutations were identified by ctDNA in 51.1% of patients and 34.5% had a targetable mutation eligible for the treatment cohorts.[20] The outcomes in patients with targetable mutations who entered the treatment cohorts were similar to previous studies involving tissue testing, supporting the clinical validity of ctDNA testing for the identification of mutations as an alternative to tissue testing.[20]

The INAVO120 trial assessed the activity of inavolisib, a phosphoinositide 3-kinase (PI3K) inhibitor, in patients with advanced PIK3CA-mutated hormone receptor-positive/HER2-negative breast cancer.[21] Both ctDNA testing and tumour biopsy sequencing (using the *PIK3CA* Mutation Test, F. Hoffmann-La Roche Ltd) were allowed for mutation identification, highlighting the clinical confidence in ctDNA testing to accurately identify this mutation. Paired ctDNA samples obtained pre- and on-treatment were compared and showed a reduction in *PIK3CA* mutation allele frequency, postulating that ctDNA may have a role as a marker of early disease response.[21]

Conclusion/Discussion

In conclusion, ctDNA can detect molecular recurrences in early-stage breast cancer before conventional imaging techniques. Patients can become ctDNA-positive at different times throughout their treatment journey, with some lead time prior to radiological relapse in a proportion of patients. With multiple trials using different testing schedules and platforms, the optimal approach in terms of timing and type of test remains to be clearly defined. The lead time between ctDNA detection and radiological progression may differ between breast cancer subtypes and, more importantly, based on the assay's sensitivity, which will need to be factored into ctDNA testing approaches. The role of ctDNA in clinical practice in early-stage breast cancer is evolving with a current lack of knowledge on whether systemic treatment(s) after detection of molecular relapses leads to the elimination of detectable ctDNA and improves outcomes rather than simply contributing to lead time bias.

CtDNA demonstrates a strong prognostic ability in the metastatic setting, as rising ctDNA levels often precede radiologic progression. However, its clinical utility in guiding treatment changes is evolving as an established standard practice. ctDNA testing is becoming common in clinical practice where assay acquisition and access to appropriately matched targeted agent(s) is available. With metastatic disease, ctDNA testing can offer a non-invasive alternative to tissue biopsies for identifying mutations and may provide more comprehensive information regarding clonality, markers of treatment resistance, and potential treatment targets.

Ultimately, while ctDNA has proven to be a valuable tool for disease monitoring, more robust clinical trials are needed to establish its definitive role in guiding treatment decisions and improving long-term survival for patients with breast cancer before it will become more entrenched into everyday clinical practice.

Correspondence

Stephen K. L. Chia, MD, FRCPC
Email: schia@bccancer.bc.ca

Financial Disclosures

M.L.: None declared.
S.C.: None declared.

References

1. Loibl S, André F, Bachelot T, Barrios CH, Bergh J, Burstein HJ, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(2):159-82.
2. Panet F, Papakonstantinou A, Borrell M, Vivancos J, Vivancos A, Oliveira M. Use of ctDNA in early breast cancer: analytical validity and clinical potential. NPJ Breast Cancer. 2024;10(1):50.
3. Moding EJ, Nabet BY, Alizadeh AA, Diehn M. Detecting Liquid Remnants of Solid Tumors: Circulating Tumor DNA Minimal Residual Disease. Cancer Discov. 2021;11(12):2968-86.
4. Garcia-Murillas I, Chopra N, Comino-Méndez I, Beaney M, Tovey H, Cutts RJ, et al. Assessment of Molecular Relapse Detection in Early-Stage Breast Cancer. JAMA Oncol. 2019;5(10):1473-8.
5. Coombes RC, Page K, Salari R, Hastings RK, Armstrong A, Ahmed S, et al. Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. Clin Cancer Res. 2019;25(14):4255-63.
6. Radovich M, Jiang G, Hancock BA, Chitambar C, Nanda R, Falkson C, et al. Association of Circulating Tumor DNA and Circulating Tumor Cells After Neoadjuvant Chemotherapy With Disease Recurrence in Patients With Triple-Negative Breast Cancer: Preplanned Secondary Analysis of the BRE12-158 Randomized Clinical Trial. JAMA Oncol. 2020;6(9):1410-5.
7. Magbanua MJM, Swigart LB, Wu HT, Hirst GL, Yau C, Wolf DM, et al. Circulating tumor DNA in neoadjuvant-treated breast cancer reflects response and survival. Ann Oncol. 2021;32(2):229-39.
8. Stecklein SR, Kimler BF, Yoder R, Schwensen K, Staley JM, Khan QJ, et al. ctDNA and residual cancer burden are prognostic in triple-negative breast cancer patients with residual disease. NPJ Breast Cancer. 2023;9(1):10.
9. Loi S, Johnston SRD, Arteaga CL, Graff SL, Chandarlapaty S, Goetz MP, et al. Prognostic utility of ctDNA detection in the monarchE trial of adjuvant abemaciclib plus endocrine therapy (ET) in HR+, HER2-, node-positive, high-risk early breast cancer (EBC). J Clin Oncol. 2024;42(17_suppl):LBA507-LBA.
10. Sherene Loi SRDJ, Carlos L. Arteaga, Stephanie L. Graff, Sarat Chandarlapaty, Matthew P. Goetz, Christine Desmedt, Hironobu Sasano, Deli Liu, Vanessa Rodrik-Outmezguine, Anthony Sireci, Cynthia Sandoval, Helen H Won, Lacey M Litchfield, Nicholas C. Turner, editor Prognostic utility of ctDNA detection in the monarchE trial of adjuvant abemaciclib plus endocrine therapy (ET) in HR+, HER2-, node-positive, high-risk early breast cancer (EBC). ASCO; 2024; Chicago, USA.
11. Pusztai L, Kalashnikova E, Hobbs E, Brown-Glaberman U, Mita M, Klein P, et al. Abstract PS06-02: Circulating tumor DNA (ctDNA) monitoring of estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) high risk breast cancer during adjuvant endocrine therapy. Cancer Res. 2024;84:PS06-2.
12. Turner NC, Swift C, Jenkins B, Kilburn L, Coakley M, Beaney M, et al. Results of the c-TRAK TN trial: a clinical trial utilising ctDNA mutation tracking to detect molecular residual disease and trigger intervention in patients with moderate- and high-risk early-stage triple-negative breast cancer. Ann Oncol. 2023;34(2):200-11.
13. Turner N, Cescon D, Loibl S, Janni W, Rugo H, Balmaña J, et al. Abstract OT2-24-02: ZEST: Randomized phase III study evaluating efficacy and safety of niraparib in patients with HER2-negative BRCA-mutated or triple-negative breast cancer with detectable circulating tumor DNA after definitive therapy. Cancer Res. 2022;82:OT2-24.
14. Turner N. Circulating tumor DNA surveillance in ZEST, a randomized, phase 3, double-blind study of niraparib or placebo in patients w/ triple-negative breast cancer or HER2+ BRCA-mutated breast cancer with molecular residual disease after definitive therapy. SABC; San Antonio Texas 2024.
15. Sant M, Bernat-Peguera A, Felip E, Margelí M. Role of ctDNA in Breast Cancer. Cancers (Basel). 2022;14(2).
16. Dickinson K, Sharma A, Agnihotram R-KV, Altuntur S, Park M, Meterissian S, et al. Circulating Tumor DNA and Survival in Metastatic Breast Cancer: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7(9):e2431722-e.
17. Wongchenko MJ, Kim SB, Saura C, Oliveira M, Lipson D, Kennedy M, et al. Circulating Tumor DNA and Biomarker Analyses From the LOTUS Randomized Trial of First-Line Ipatasertib and Paclitaxel for Metastatic Triple-Negative Breast Cancer. JCO Precis Oncol. 2020;4:1012-24.
18. Smerage JB, Barlow WE, Hortobagyi GN, Winer EP, Leyland-Jones B, Srkalovic G, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. 2014;32(31):3483-9.
19. Appierto V, Di Cosimo S, Reduzzi C, Pala V, Cappelletti V, Daidone MG. How to study and overcome tumor heterogeneity with circulating biomarkers: The breast cancer case. Semin Cancer Biol. 2017;44:106-16.
20. Turner NC, Kingston B, Kilburn LS, Kernaghan S, Wardley AM, Macpherson IR, et al. Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. Lancet Oncol. 2020;21(10):1296-308.
21. Jhaveri KL, Accordino MK, Bedard PL, Cervantes A, Gambardella V, Hamilton E, et al. Phase I/Ib Trial of Inavolisib Plus Palbociclib and Endocrine Therapy for PIK3CA-Mutated, Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced or Metastatic Breast Cancer. J Clin Oncol. 2024;42(33):3947-56.

About the Authors

Lorena A. Mija

Lorena A. Mija is a medical student at Université de Montréal with a passion for community health, patient advocacy, and oncology research. She is dedicated to improving healthcare accessibility through outreach initiatives and public engagement.

Affiliations: Faculté de médecine, Université de Montréal, Montréal, QC, Canada

Arielle Elkrief, MD, FRCPC

Dr. Arielle Elkrief is an Assistant Professor in the Department of Hematology & Oncology at the Centre hospitalier de l'Université de Montréal (CHUM) and serves as Co-Director of the CHUM Microbiome Centre. As a clinician-scientist, Dr. Elkrief specializes in the care of patients with lung cancer and melanoma. During her fellowship at Memorial Sloan Kettering Cancer Center under the mentorship of Dr. Charles Rudin, she contributed to the discovery that the tumor microbiome influences response to immunotherapy. In addition, her work demonstrated the negative role of antibiotics on immunotherapy activity. Dr. Elkrief's research program now focuses on developing clinical trials to positively change the gut microbiome in patients with lung cancer and melanoma using fecal microbiota transplantation, prebiotics, and diet. In addition, her research laboratory focuses on discovering novel biomarkers of response to immunotherapy using the gut and tumor microbiomes. Dr. Elkrief was recently awarded the American Society of Clinical Oncology Young Investigator Award and Society of Immunotherapy of Cancer Women in Melanoma Award, and has published over 78 peer-reviewed publications.

Affiliations: Axe Cancer, Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC, Canada
Hemato-Oncology Division, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada

doi.org/10.58931/cot.2025.2131

Clinical Considerations for the Management of Advanced PD-L1 ≥50% Non-small Cell Lung Cancer In 2025: Should All Patients Be Treated the Same?

Lorena A. Mija
Arielle Elkrief, MD, FRCPC

Non-small Cell Lung Cancer with PD-L1 Tumour Proportion Score ≥50%

Despite advances in the treatment of non-small cell lung cancer (NSCLC) due to the advent of immunotherapy in the form of immune checkpoint inhibitors (ICI), NSCLC remains the leading cause of cancer-related death in Canada.[1] In addition, multiple first-line options exist for patients with NSCLC without a sensitizing mutation in epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*), but no head-to-head comparisons of first-line treatment regimens have been made in randomized controlled trials. The programmed cell death ligand 1 (PD-L1) tumour proportion score (TPS)—which is derived from immunohistochemistry analysis—emerged as an important biomarker early in the advent of ICI in NSCLC. Approximately 30% of patients with NSCLC have PD-L1 expression in at least 50% of the tumour.[1] This ≥50% threshold was established through retrospective biomarker analyses in pivotal trials, such as the KEYNOTE-001[2] and KEYNOTE-024 trials,[3] in which patients with higher PD-L1 expression demonstrated superior response rates and overall survival (OS) benefits with immunotherapy compared to chemotherapy. The KEYNOTE-001 trial first identified ≥50% PD-L1 expression as an optimal cut-off for predicting response to pembrolizumab (anti-programmed cell death protein 1 [PD-1] antibody), showing an objective response rate (ORR) of ~45% in this group. Subsequently, the KEYNOTE-024 trial confirmed that patients with PD-L1 ≥50% had significantly improved progression-free survival (PFS) and OS with pembrolizumab than those treated with chemotherapy (hazard ratio [HR] for PFS: 0.50, 95% confidence interval [CI]: 0.37–0.68). Similar findings from the IMpower110[4] (atezolizumab) and EMPOWER-Lung 1[5] trials (cemiplimab) reinforced ≥50% PD-L1 TPS as a clinically meaningful biomarker. As a result, ≥50% PD-L1 TPS became an actionable biomarker in regulatory approvals and treatment guidelines, guiding immunotherapy decisions in advanced NSCLC.

ICI Monotherapy

Randomized controlled trials have demonstrated that ICI monotherapy consisting of pembrolizumab, atezolizumab, or cemiplimab, is an excellent first-line treatment option for patients with high (≥50%) PD-L1 TPS NSCLC without an actionable driver. ICI demonstrated benefits in ORR, PFS, and OS compared to chemotherapy. The use of pembrolizumab in patients with a PD-L1 TPS ≥50% is supported by the Phase III KEYNOTE-024 trial, which randomized 305 treatment-naïve patients with advanced NSCLC to receive either pembrolizumab monotherapy or platinum-doublet chemotherapy.[6] Pembrolizumab significantly improved PFS compared to chemotherapy (median PFS: 10.3 vs. 6 months; HR: 0.50, 95% CI: 0.37–0.68) and had a higher ORR

(45% vs. 28%).[3] At 5 years of follow-up, pembrolizumab demonstrated improved OS compared to chemotherapy (median OS: 26.3 vs. 13.4 months; HR: 0.62, 95% CI: 0.48–0.81).[7] The addition of ipilimumab (anti-cytotoxic T lymphocyte-associated protein 4 [CTLA-4]) to pembrolizumab did not improve efficacy and increased toxicity.[8] Atezolizumab (anti-PD-L1) in this patient population was studied as part of the IMpower110 trial, which included 572 patients with treatment-naïve stage IV NSCLC with PD-L1 expression. This study demonstrated that among 205 patients with high PD-L1 expression, atezolizumab improved OS compared to platinum-based chemotherapy (20.2 vs. 13.1 months; HR: 0.59, 95% CI: 0.40–0.89).[9] Median PFS was also superior with atezolizumab (8.1 vs. 5.0 months; HR: 0.63, 95% CI: 0.45–0.88), and the ORR was higher (38% vs. 29%).[9] Lastly, cemiplimab (anti-PD-1), was evaluated in the EMPOWER-Lung 1 trial, which enrolled 565 patients with NSCLC and PD-L1 expression of at least 50%, and showed that cemiplimab improved OS compared to platinum-doublet chemotherapy at a 35-month follow-up (26.1 vs. 13.3 months; HR: 0.57, 95% CI: 0.46–0.71).[10] None of these regimens have been compared head-to-head, but pembrolizumab has the advantage of having approval to be administered every 6 weeks, which is preferred for some patients over the 3 week intervals which require more frequent visits to the hospital. Severe grade ≥3 adverse events in response to single agent anti-PD(L)-1 therapy occur in 10–30% of patients.[1]

ICI in Combination with Platinum-Doublet Chemotherapy

The KEYNOTE-189 trial enrolled 616 patients with metastatic non-squamous NSCLC, who were randomized to receive either a combination of pembrolizumab, pemetrexed, and platinum-based chemotherapy, or placebo plus pemetrexed and platinum-based chemotherapy.[11] Patients were stratified based on PD-L1 expression (TPS ≥1% vs. <1%), with further division of the PD-L1 ≥1% group into PD-L1 1–49% and ≥50% subgroups. The trial demonstrated superior outcomes for the pembrolizumab combination therapy in all PD-L1 subgroups compared to standard chemotherapy. In the TPS ≥50% subgroup (N=202), the pembrolizumab combination therapy resulted in a one-year OS rate of 73% vs. 48% for placebo plus chemotherapy (HR: 0.42), with an ORR of 61.4% vs. 22.9%. An updated analysis at 5 years of follow-up demonstrated continued OS benefit in the PD-L1 ≥50% subgroup (29.6 vs. 21.4 months, HR: 0.68).[12]

Similarly, the KEYNOTE-407 trial focused on metastatic squamous NSCLC and demonstrated improved outcomes with pembrolizumab and chemotherapy compared to chemotherapy alone.[13] The combination therapy resulted in an ORR of 58.4% vs. 35.0% (P=0.0004) and a median OS of 15.9 versus 11.3 months (HR: 0.64, P=0.0008). Among patients with a PD-L1 TPS ≥50%, the one-year survival rate was 63.4% versus 51.0% (HR: 0.64), with continued benefit at 5 years (23.3 vs. 8.3 months, HR: 0.68).[14] These findings from the KEYNOTE-189 and KEYNOTE-407 trials indicate that combination chemoimmunotherapy is effective as a first-line treatment for both metastatic squamous and non-squamous NSCLC, regardless of PD-L1 expression. Notably, the PD-L1 ≥50% subgroup exhibited a stronger therapeutic response across both trials. Nevertheless, the combination across all studies was associated with grade ≥3 adverse events in 50–70% of patients.[1]

Should all Patients with NSCLC with High PD-L1 Expression Be Treated the Same?

A direct comparison between ICI monotherapy and a combination of ICI with chemotherapy in patients with PD-L1-high NSCLC has not been conducted in a randomized controlled trial. However, indirect evidence from existing studies, retrospective studies, and meta-analyses provides insights into their relative efficacy.

A meta-analysis of 5 randomized trials indicated that the combination of pembrolizumab and chemotherapy led to superior ORR compared to pembrolizumab monotherapy (relative risk: 1.6, 95% CI: 1.2–2.2) and improved PFS (HR: 0.55, 95% CI: 0.32–0.97). However, there was not a statistically significant difference in OS between the two approaches (HR: 0.76, 95% CI: 0.51–1.14).[15]

Another analysis that included data from 12 trials, of which half evaluated chemoimmunotherapy and the other half immunotherapy monotherapy in patients with PD-L1 expression ≥50%, found that the median PFS was longer for chemoimmunotherapy than immunotherapy monotherapy (9.6 vs. 7.1 months, HR: 0.69, 95% CI: 0.55–0.87). Additionally, the ORR was higher in the chemoimmunotherapy

group (61% vs. 43%). While OS showed a trend toward improvement with chemoimmunotherapy (HR: 0.82), it did not reach statistical significance. Furthermore, among patients aged 75 years or older, there was a nonsignificant trend toward worsened survival with chemoimmunotherapy (HR: 1.7).[16]

Some clinicians consider the ORR and PFS advantage of adding chemotherapy to immunotherapy compelling, especially in patients with symptomatic disease, high disease burden, or rapidly progressive disease, while others argue that the absence of a clear OS benefit supports the use of immunotherapy alone in this selected patient population. The choice between these strategies may depend on patient-specific factors, including disease burden, comorbidities, and treatment goals. For those whose tumours have ≥50% PD-L1 TPS and a low risk of symptomatic decline if treatment is ineffective, either ICI monotherapy or chemoimmunotherapy are appropriate. Patients who value minimizing time and toxicity of treatment may choose immunotherapy monotherapy, while patients who value delayed time to progression may opt for chemoimmunotherapy.

Real-world retrospective data have also aimed to solve this conundrum—in a large analysis from Memorial Sloan Kettering and the Dana Farber Cancer Institute, our group retrospectively analyzed 866 patients treated with immunotherapy or chemoimmunotherapy in the first-line setting.[17] Relative to immunotherapy, and similar to previously shown results, chemoimmunotherapy was associated with improved ORR and PFS, but not OS, in the PD-L1 TPS ≥50% subgroup. Using propensity-adjusted analyses, only never-smokers in the PD-L1 TPS ≥50% subgroup derived a differential survival benefit from chemoimmunotherapy vs. immunotherapy. Among patients with very high PD-L1 TPS (≥90%), there were no differences in outcome between treatment groups, suggesting that immunotherapy alone may be sufficient in this subgroup. These results corroborated earlier findings by Perrol et al.[18]

Conclusions

The clinical trial results reviewed here highlight that the addition of chemotherapy to immunotherapy increases the probability of an initial response in a heterogeneous patient population with differential sensitivity to chemotherapy and immunotherapy. However, long-term benefit appears largely driven by whether PD-L1 blockade generates durable antitumour immunity. Retrospective data, which have inherent limitations, demonstrate that chemoimmunotherapy should be considered for never-smokers, even in the presence of high PD-L1 expression. It is possible that the advantage observed for chemoimmunotherapy in the never-smoker population with PD-L1 TPS ≥50%, might represent a subset of NSCLC, which, although it is genomically negative for drivers such as EGFR or ALK, may be a group of patients whose cancer has yet unidentified drivers, for which existing data suggests inferior immunotherapy response. For example, several studies have identified oncogenic fusions using RNA sequencing in patients without a driver alteration identified through targeted next-generation sequencing (NGS) methods, highlighting the importance of broad NGS profiling in the clinic. Lastly, emerging biomarkers, such as the gut microbiome,[19] and artificial intelligence (AI)-based analysis of pathology slides,[20] may further help tailor treatment decisions.

Correspondence

Arielle Elkrief, MD, FRCPC
Email: arielle.elkrief@umontreal.ca

Financial Disclosures

L.M.: None declared.
A.E.: Consulting fees: Merck, AstraZeneca, and BMS; **Research support:** AstraZeneca, Merck, and Kanvas Biosciences.

References

1. Elkrief A, Joubert P, Florescu M, Tehfe M, Blais N, Routy B. Therapeutic landscape of metastatic non-small-cell lung cancer in Canada in 2020. Curr Oncol. 2020;27(1):52-60.
2. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2015;372(21):2018-28.
3. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2016;375(19):1823-33.
4. Herbst RS, Giaccone G, Marinis Fd, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. New England Journal of Medicine. 2020;383(14):1328-39.
5. Sezer A, Kilickap S, Gümüş M, Bondarenko I, Özgüroğlu M, Gogishvili M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. The Lancet. 2021;397(10274):592-604.
6. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823-33.
7. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021;39(21):2339-49.
8. Boyer M, Şendur MAN, Rodríguez-Abreu D, Park K, Lee DH, Çiçin I, et al. Pembrolizumab Plus Ipilimumab or Placebo for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study. J Clin Oncol. 2021;39(21):2327-38.
9. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med. 2020;383(14):1328-39.
10. Ozguroglu M, Kilickap S, Sezer A, Gumus M, Bondarenko I, Gogishvili M, et al. First-line cemiplimab monotherapy and continued cemiplimab beyond progression plus chemotherapy for advanced non-small-cell lung cancer with PD-L1 50% or more (EMPOWER-Lung 1): 35-month follow-up from a mutlicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(9):989-1001.
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, Angelis FD, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2018;378(22):2078-92.
12. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non–Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. Journal of Clinical Oncology. 2023;41(11):1992-8.
13. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2018;379(21):2040-51.
14. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. J Clin Oncol. 2023;41(11):1999-2006.
15. Zhou Y, Lin Z, Zhang X, Chen C, Zhao H, Hong S, et al. First-line treatment for patients with advanced non-small cell lung carcinoma and high PD-L1 expression: pembrolizumab or pembrolizumab plus chemotherapy. J Immunother Cancer. 2019;7(1):120.
16. Akinboro O, Vallejo JJ, Nakajima EC, Ren Y, Mishra-Kalyani PS, Larkins EA, et al. Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis. Journal of Clinical Oncology. 2022;40(16_suppl):9000-.
17. Elkrief A, Alessi JMV, Ricciuti B, Brown S, Rizvi H, Preeshagul IR, et al. Efficacy of PD-(L)1 blockade monotherapy compared with PD-(L)1 blockade plus chemotherapy in first-line PD-L1-positive advanced lung adenocarcinomas: a cohort study. J Immunother Cancer. 2023;11(7).
18. Pérol M, Felip E, Dafni U, Polito L, Pal N, Tsourti Z, et al. Effectiveness of PD-(L)1 inhibitors alone or in combination with platinum-doublet chemotherapy in first-line (1L) non-squamous non-small-cell lung cancer (Nsq-NSCLC) with PD-L1-high expression using real-world data. Ann Oncol. 2022;33(5):511-21.
19. Elkrief A, Derosa L, Kroemer G, Zitvogel L, Routy B. The negative impact of antibiotics on outcomes in cancer patients treated with immunotherapy: a new independent prognostic factor? Ann Oncol. 2019;30(10):1572-9.
20. Prelaj A, Miskovic V, Zanitti M, Trovo F, Genova C, Viscardi G, et al. Artificial intelligence for predictive biomarker discovery in immuno-oncology: a systematic review. Annals of Oncology. 2024;35(1):29-65.

About the Authors

Jie Wei Zhu, MD

Dr. Zhu is an incoming Medical Oncology Resident at the University of Toronto and will be completing her Internal Medicine training starting in July 2025 also at the University of Toronto. Her professional interests include breast, gynecologic, and gastrointestinal malignancies, and she hopes to pursue further research training in clinical research methodology or molecular genetics.

Affiliations: Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Ines B. Menjak, MD

Dr. Ines Menjak is a staff medical oncologist at Sunnybrook Health Sciences Centre. She completed her medical training at the University of Toronto and has a Master's of Science in Health Research Methodology, Clinical Epidemiology Stream from McMaster University. She specializes in skin cancer and thoracic cancer. She is the founder and lead of the Geriatric Oncology Clinic at Sunnybrook. She is also the head of the Lung Clinical Trials Group. Her research focuses on improving the care of older patients with cancer, as well as immunotherapy toxicity.

Affiliations: Department of Medicine, Division of Medical Oncology and Hematology, University of Toronto, Toronto, Ontario, Canada
Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Arjun Sahgal, BSc, MD, FRCPC

Dr. Arjun Sahgal is an international clinical and research leader in the field of high precision stereotactic radiation to the brain and spine for both metastases and primary tumors. He currently serves as the Chief of the Department of Radiation Oncology at the University of Toronto affiliated Sunnybrook Odette Cancer Centre. Since his radiation oncology training at the University of Toronto and fellowship at the University of California San Francisco, he has published over 600 peer reviewed papers in high impact journals like the Journal of Clinical Oncology, Lancet Oncology and New England Journal of Medicine, and 40 international guidelines specific to SRS and SBRT. He has given over 200 lectures as an invited international speaker. He invented the 24 Gy in 2 SBRT fractions regimen for spinal metastases which was tested in his landmark international CCTG SC24 randomized trial, proving superiority over conventional palliative radiation with respect to complete pain response. He has been instrumental in raising ~$50M in grant and philanthropic funding to support central nervous system research at Sunnybrook. In addition to leading several international research consortia, he has served as co-Chairperson of the AOSpine Tumour Knowledge Forum, and is currently the President of the International Stereotactic Radiosurgery Society (ISRS). His next phase of research is in the development of advanced MR in CNS radiation therapy, MR Linac adaptive RT for GBM, CT-adaptive radiotherapy, and automated vertebral fracture risk prediction. In addition, he leads the Canadian randomized trial of SBRT vs. conventional radiation for non-spine bone metastases (CCTG SC-29).

Affiliations: Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

doi.org/10.58931/cot.2025.2132

Katarzyna J. Jerzak, MD, MSc, FRCPC

Dr. Katarzyna Jerzak is a Medical Oncologist and Clinician Investigator at the Sunnybrook Odette Cancer Center and Assistant Professor at the University of Toronto. She is also an Associate Scientist at the Sunnybrook Research Institute and Lead of breast oncology clinical trials at her Centre. Dr. Jerzak's research focus is related to clinical trials and brain metastases. She is a member of international clinical trials organizations, including the breast committee within NRG Oncology and the Breast International Group (BIG) Brain Metastases Task Force. She is also actively participating in the National Cancer Institute's National Clinical Trials Network (NCTN)-BIG Core Working Group regarding brain metastases and is a core member of the Canadian "REAL" Breast Cancer Alliance. Dr. Jerzak has over 100 publications, including publications in high impact journals such as Lancet Oncology, JAMA Oncology, and Clinical Cancer Research.

Affiliations: Department of Medicine, Division of Medical Oncology and Hematology, University of Toronto, Toronto, Ontario, Canada
Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Current Approaches and Future Directions for the Treatment of Solid Tumour Brain Metastases

Jie Wei Zhu, MD
Ines B. Menjak, MD
Arjun Sahgal, BSc, MD, FRCPC
Katarzyna J. Jerzak, MD, MSc, FRCPC

Introduction

Brain metastases (BrM) are most common among patients with metastatic lung cancer, breast cancer, and melanoma.[1] Historically, management of BrM consisted of local treatments with surgical resection and/or radiation therapy, with either whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS). Current guidelines recommend SRS as the initial therapy for patients who have up to four BrM,[2] but several studies have demonstrated that upfront SRS may be considered for some patients who have more than four BrM given additional clinical benefits of improved memory function and quality of life compared to WBRT.[3-5]

Systemic therapies are increasingly understood to cross the blood-brain barrier (BBB) following disruption of its integrity upon BrM development. Disseminated tumour cells intravasate into the circulation and spread hematogenously with a "seed and soil" tropism for the brain that provides a suitable tumour microenvironment.[6,7] Tumour cells extravasate and increase the permeability of the BBB by decreasing tight junction protein expression, decreasing astrocyte pedicles, reducing pericyte coverage, and increasing neoangiogenesis.[8] The altered integrity of the BBB allows penetration of large drug molecules, such as antibody-drug conjugates (ADCs), which exert their therapeutic effects by binding to tumour cell-specific epitopes and releasing a cytotoxic payload, even in the absence

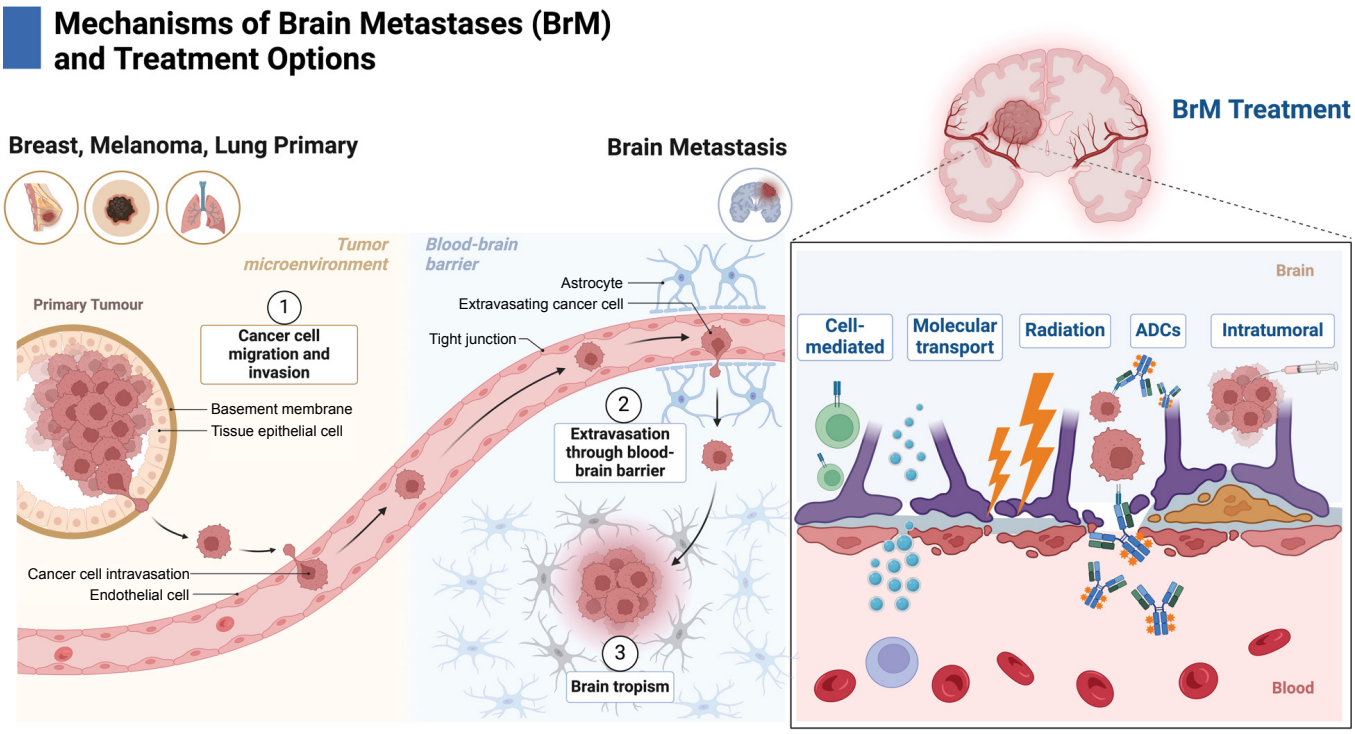

Figure 1. Schematic illustrating the mechanisms by which primary tumours metastasize to the brain and mechanism of action for various therapies, including cell-mediated transport, molecular transport, physical disruption (i.e., radiation), antibody-drug conjugate epitope recognition, and intratumoral drug delivery; *created with Biorender.com.*

Abbreviations: BrM: brain metastases, **ADCs:** antibody-drug conjugates

of radiation.[9] Other therapeutic mechanisms of action include molecular (passive or receptor-mediated transport), physical (radiation or focused ultrasound), direct delivery to the brain (intrathecal or intratumoral), and cell-mediated (immune cell extravasation) (**Figure 1**).[8,9]

Several novel small-molecule tyrosine kinase inhibitors (TKIs) have been developed for the treatment of driver mutation-positive lung cancer, which is associated with the highest risk of BrM. Novel anaplastic lymphoma kinase (ALK) inhibitors, including crizotinib, alectinib, brigatinib, and lorlatinib, have led to a breakthrough in the treatment of patients with ALK-mutant non-small cell lung cancer (NSCLC) and BrM.[10-13] The phase III CROWN trial compared lorlatinib to crizotinib in advanced ALK-positive NSCLC and included 78 (26.4%) patients with active BrM, among whom 30 patients (10.1%) had measurable disease.[13] This study found that patients treated with lorlatinib had a significantly higher intracranial objective response rate (IC-ORR) compared to those receiving crizotinib (66% vs. 20%); the complete intracranial response rate was much higher among patients receiving lorlatnib as well (61% vs. 15%). In addition, only 4 out of the 114 patients (3%) without BrM at baseline in the lorlatinib group later developed BrM; this is much lower than 33% of patients who developed BrM in the crizotinib arm of this trial.[13] Altogether, the evidence suggests that lorlatinib not only controls existing BrM but may also prevent the development of new BrM.

Similarly, there is evidence supporting the use of osimertinib for the treatment of BrM among patients with epidermal growth factor receptor (EGFR)-mutant metastatic NSCLC. A systematic review and meta-analysis that included 15 studies with 324 patients reported an IC-ORR rate of 64% (95% confidence interval [CI] = 53–76%; n = 195) and complete intracranial response rates of 7% to 23%.[14] The median duration of central nervous system (CNS) response among included studies ranged from 8.9 to 15.2 months. A recent multi-centre retrospective study examining

317 TKI-naïve patients with EGFR- and ALK-mutant NSCLC with BrM found that the addition of upfront SRS to TKI treatment prolonged time to CNS progression versus TKI treatment alone. Local CNS control was significantly improved with the use of both TKI and SRS (hazard ratio [HR] = 0.30, 95% CI = 0.16–0.55, P <.001) versus TKI alone, and the cumulative incidence of CNS progression at 24 months was 9% vs. 25%, respectively.[15] However, there was no significant difference in overall survival (OS).[15] This lack of survival detriment with omission of brain radiotherapy has motivated a phase II Canadian-led trial that is currently underway to determine the impact of SRS plus osimeritnib versus osimeritnib alone for patients with treatment-naïve EGFR-mutant metastatic NSCLC with BrM (NCT03769103). These results are eagerly anticipated to better understand which patients with EGFR-mutant metastatic NSCLC can safely avoid upfront brain radiation (and its associated toxicities) for newly diagnosed BrM. For locally advanced disease, the LAURA trial that randomized 216 patients with Stage III EGFR-mutated NSCLC to osimertinib versus placebo following chemoradiation and found that the incidence of new brain lesions was much lower at 8% in the osimertinib group compared to 29% with placebo.[16]

Another important setting where TKIs have demonstrated significant benefit among patients with BrM is HER2⁺ metastatic breast cancer (MBC).[17,18] The strongest data come from the randomized HER2CLIMB trial that demonstrated a survival benefit associated with the addition of tucatinib to capecitabine/trastuzumab among patients with active or treated stable BrM compared to those receiving capecitabine and trastuzumab alone.[19] This study included 291 patients (48%) with HER2⁺ MBC and BrM, among whom 60% had active BrM, defined as previously untreated or treated but progressing BrM at time of enrolment. Patients with BrM who received tucatinib also had a longer median OS than those who did not (22 vs. 13 months; HR = 0.60, 95% CI = 0.44–0.81), which was similar to the overall study population. Furthermore, the median new brain lesion-free survival was 11.1 months longer among tucatinib-treated patients (24.9 vs. 13.8 months, respectively, p = 0.006). This study reflects an emerging shift in the design of clinical trials to include patients with active BrM, with the safety of this approach to date allowing for major advancements in the treatment of patients with HER2⁺ MBC.

For patients with HER2⁺ MBC and BrM, treatment with HER2-directed ADCs may also be an option. The first available ADC for patients with HER2⁺ MBC was trastuzumab emtansine (T-DM1), which showed intracranial efficacy in the KAMILLA phase IIIB clinical trial.[20] Among 2,002 patients with HER2⁺ MBC, 398 (19.9%) had BrM at baseline.[20] A ≥30% reduction in the "sum of the major diameters" of BrM was observed for ~43% of the overall cohort and for ~49% of those (n=67, 16.8%) who did not receive prior brain radiotherapy. Since then, trastuzumab deruxtecan (T-DXd) has demonstrated a 73.3% IC-ORR in patients with HER2⁺ MBC and active BrM (n= 15 patients in the intention-to-treat population),[21] as well as an impressive IC-ORR of 45% in a pooled analysis of the DESTINY-Breast-01, -02, and -03 clinical trials.[22] More recently, the DESTINY-Breast-12 trial that included 263 patients with MBC and stable or active BrM and previously treated with anti-HER2 therapy reported a CNS PFS of 58.9% and CNS ORR of 71.7%.[23]

Additional systemic therapies with demonstrated efficacy for treating BrM include immune checkpoint inhibitors and BRAF/MEK inhibitors that are frequently used to treat patients with metastatic melanoma. Approximately 25% of patients have BrM at the time of melanoma diagnosis, and up to 75% of patients will eventually develop BrM during their lifetime.[19] Clinical trials examining the combination of ipilimumab and nivolumab for patients with metastatic melanoma and asymptomatic BrM established this combination to be a valuable treatment with intracranial response rates over 50%.[24,25] The CheckMate-204 trial reported an IC-ORR of 55% among 101 patients with melanoma and asymptomatic BrM, and 17% among 18 patients with symptomatic BrM.[24] BRAF V600E-mutated melanoma is associated with a higher risk of BrM; for this population, therapies targeting BRAF and MEK (i.e. dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib) have been approved as the standard of care usually after disease progression on immunotherapy.[26] BRAF/MEK inhibitor combinations cross the BBB, and are associated with intracranial response rates of up to 59% for oral dabrafenib plus trametinib among patients with BRAFV600E-positive metastatic melanoma and asymptomatic BrM.[27] A recent randomized trial examining the combination of relatlimab, a lymphocyte activation gene-3 (LAG-3)-blocking antibody, and nivolumab in patients with treatment-naïve unresectable Stage III or IV melanoma reported a 4% decrease

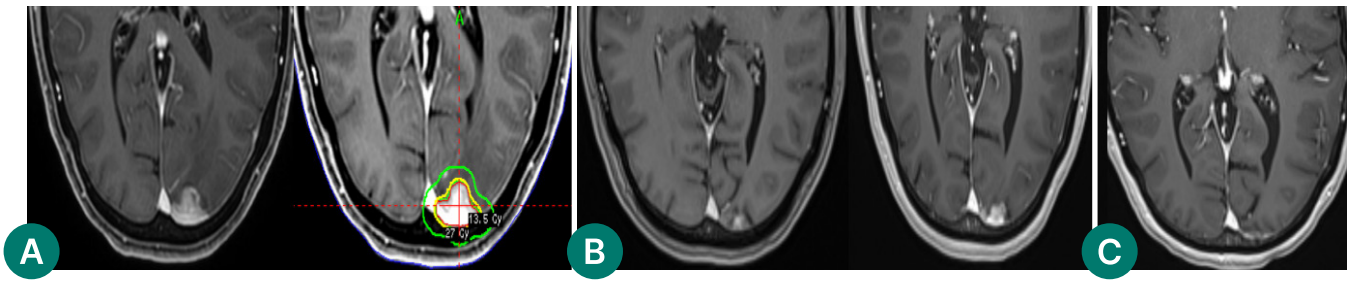

Figure 2. (A) Patient with HER2⁺ (IHC 3+) breast cancer with a brain metastasis treated with SRS (27 Gy in 3 fractions) with good response. **(B)** Two years later while continuing trastuzumab/pertuzumab had evidence of growth with perfusion imaging suggesting recurrence. **(C)** Following 3 cycles of trastuzumab deruxtecan a dramatic response is observed; *courtesy of Jie Wei Zhu, MD, Ines B. Menjak, MD, Arjun Sahgal, BSc, MD, FRCPC, and Katarzyna J. Jerzak, MD, MSc, FRCPC*.

Abbreviations: IHC: immunohistochemistry, **SRS:** stereotactic radiosurgery

in the frequency of new CNS metastases with relatlimab and nivolumab compared to nivolumab alone (5% vs. 9%, respectively).[27] Further, this study found that relatlimab and nivolumab extended the median time to development of CNS metastases from 6.6. months to 11.1 months.[28]

While there is optimism for the use of systemic therapies for BrM, it is prudent to be cautious and adopt a multi-disciplinary approach to treatment with review by neurosurgeons, CNS radiation oncologists, and medical oncologists. There are several factors to consider when selecting the best treatment approach, including patient factors (i.e., number and location of BrM, patients' neurological symptoms and functional status), tumour biology (biomarker status and likelihood of IC-ORR), and prior treatment history. In some cases, multimodal treatment may be an option; however, in cases where radiation has already been maximized, systemic therapy may be a more attractive option, but has been poorly studied in this setting (**Figure 2**). The use of systemic therapies first is attractive as this is a strategy that can potentially avoid radiation-associated toxicities, such as radiation necrosis. This may be of particular concern with the advent of ADCs, which are associated with an increased risk of symptomatic radiation necrosis with a 2-year risk of 42% for patients with HER2⁺ MBC receiving trastuzumab deruxtecan or sacituzumab govitecan concurrently with SRS; in contrast, the risk of radiation necrosis is much lower (only 9%) when ADCs and radiation therapy are used sequentially.[29] Another retrospective study including 67 patients with HER2⁺ breast cancer with BrM also reported a significantly higher risk of radiation necrosis associated with T-DM1 exposure following SRS (p =0.02), with an overall probability of post-SRS radiation necrosis of 21.6%.[30] As such, caution should be taken to mitigate the risk of radiation necrosis with the increasingly widespread usage of ADCs for other disease sites.

Future efforts should be directed towards encouraging enrolment of patients with BrM in clinical trials, especially when CNS efficacy of investigational agents is expected. This has been reviewed by Corbett et al.; while 56% of phase III clinical trials evaluating the efficacy of systemic therapies in metastatic lung cancer, breast cancer, and melanoma enroled patients with BrM, there is still room for progress.[31] Further, including patients with BrM in clinical trials may accelerate the investigation into biomarkers to enable a better understanding of the biology of BrM, predictive markers of response, and mechanisms of resistance to evaluated therapies, as well as novel therapeutic targets.[32]

Future trials should also determine whether therapies effective in the metastatic setting may have utility in the prevention of BrM. The HER2CLIMB-05 trial (NCT05132582), which is evaluating the efficacy of first-line maintenance tucatinib, will also investigate whether this small molecule TKI can reduce the incidence of BrM among patients with newly diagnosed HER2⁺ MBC. In the early-stage setting, the CompassHER2-RD trial (NCT04457596) is evaluating the addition of tucatinib to T-DM1 for patients with residual HER2⁺ breast cancer following neoadjuvant HER2-directed therapy. Therapies that can prevent the development of BrM are of significant interest and represent an important unmet need; a nomogram to predict development of BrM among

patients with various solid tumours would be of value and could help inform inclusion criteria for future prevention trials.

Another area of unmet need is the evaluation of CNS-active systemic therapies among patients with leptomeningeal disease (LMD), which are associated with a particularly short survival. A recent systematic review demonstrated that none of the 244 phase III trials reported LMD-specific outcomes and only 5.3% of studies included CNS-specific outcomes.[33] Brastianos et al. identified that single agent immune checkpoint inhibitor is an effective treatment option among patents with breast, lung, and ovarian cancer and LMD; evaluation of future combination therapies, ideally in randomized trials, would be of high interest.[34] Therapies for patients with LMD originating from breast, melanoma, and NSCLC have been recently reviewed.[35-37] The recent BLOSSOM phase II trial examining the efficacy of osimertinib among 73 patients with EGFR-mutated NSCLC who developed LMD following prior TKI therapy reported an objective response rate for LMD of 52%, although larger studies are required to validate these findings.[38] Several novel therapeutic approaches are also being investigated; examples include the use of intrathecal treatment with nivolumab and ipilimumab (NCT055988530), as well as liposomal-rhenium-186, a novel radioligand therapy that is encapsulated in nanoliposomes (NCT05034497).

Increasing attention to solid tumours that are less likely to metastasize to the brain is required. For example, patients with gastrointestinal and gynecological malignancies are living longer and may experience metastases to the brain, with an emerging need for tumour-agnostic BrM trials, particularly when systemic therapies with a high likelihood of CNS efficacy are available across different primary tumour subtypes.

Conclusion

In conclusion, BrM represent a significant challenge in the treatment of patients with solid tumours. Recent advancements in systemic therapies for BrM including TKIs, ADCs and immune checkpoint inhibitors have improved patients' outcomes. Future efforts should be directed towards understanding the molecular drivers of BrM and therapies to prevent their development.

Correspondence

Katarzyna Joanna Jerzak, MD
Email: katarzyna.jerzak@sunnybrook.ca

Financial Disclosures

J.W.Z.: None declared.
I.B.M.: None declared.
A.S.: None declared.
K.J.J.: Speaker/advisor board/consultant for: Amgen, AstraZeneca, Apo Biologix, Daiichy Sankyo, Eli Lilly, Esai, Genomic Health, Gilead Sciences, Knight Therapeutics, Merck, Myriad Genetics Inc, Pfizer, Roche, Seagen, Novartis, Organon, Viatris;
Research funding: AstraZeneca, Eli Lilly, Seagen

References

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004;22(14): 2865–2872. doi: 10.1200/JCO.2004.12.149.
2. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol 2022;40(05):492–516. doi: 10.1200/JCO.21.02314.
3. Yamamoto M, Serizawa T, Sato Y, Higuchi Y, Kasuya H. Stereotactic radiosurgery results for patients with 5-10 versus 11-20 brain metastases: a retrospective cohort study combining 2 databases totaling 2319 patients. World Neurosurg 2021;146: e479–e491. doi: 10.1016/j.wneu.2020.10.124.
4. Balasubramanian SK, Sharma M, Venur VA, et al. Impact of EGFR mutation and ALK rearrangement on the outcomes of non-small cell lung cancer patients with brain metastasis. Neuro-oncol 2020;22(02):267–277. doi: 10.1093/neuonc/noz155.
5. Sahgal A, Ruschin M, Ma L, Verbakel W, Larson D, Brown PD. Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues. Neuro Oncol. 2017;19(suppl_2):ii2-ii15. doi:10.1093/neuonc/nox001.
6. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66. doi:10.1038/s41572-019-0111-2.
7. Gwak HS. Molecular biology of brain metastases. Brain Tumor Res Treat. 2023 Jan;11(1):8-15. doi: 10.14791/btrt.2022.0045.
8. Arvanitis, C. D., Ferraro, G. B. & Jain, R. K. The blood–brain barrier and blood–tumour barrier in brain tumours and metastases. Nat Rev Cancer 20, 26–41 (2020). doi: 10.1038/s41568-019-0205-x.

9. Mair MJ, Bartsch R, Le Rhun E, et al. Understanding the activity of antibody-drug conjugates in primary and secondary brain tumours. Nat Rev Clin Oncol. 2023;20(6):372-389. doi:10.1038/s41571-023-00756-z.
10. Solomon BJ, Cappuzzo F, Felip E, et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: results from PROFILE 1014. J Clin Oncol 2016;34(24):2858–2865. doi: 10.1200/JCO.2015.63.5888.
11. Peters S, Camidge DR, Shaw AT, et al; ALEX Trial Investigators. Alectinib versus crizotinib in untreated ALK-positive non-small cell lung cancer. N Engl J Med 2017;377(09):829–838. doi: 10.1056/NEJMoa1704795.
12. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open label, phase 3 study. Lancet 2017;389(10072):917–929. doi: 10.1016/S0140-6736(17)30123-X.
13. Shaw AT, Bauer TM, de Marinis F, et al; CROWN Trial Investigators. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med 2020;383(21):2018–2029. doi: 10.1056/NEJMoa2027187.
14. Erickson AW, Brastianos PK, Das S. Assessment of effectiveness and safety of osimertinib for patients with intracranial metastatic disease: A systematic review and meta-analysis. JAMA Netw Open. 2020;3(3):e201617. doi:10.1001/jamanetworkopen.2020.1617.
15. Pike LRG, Miao E, Boe LA, et al. Tyrosine Kinase Inhibitors with and Without Up-Front Stereotactic Radiosurgery for Brain Metastases From EGFR and ALK Oncogene-Driven Non-Small Cell Lung Cancer (TURBO-NSCLC). J Clin Oncol. Published online July 24, 2024. doi:10.1200/JCO.23.02668.
16. Lu S, Kato T, Dong X, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. N Engl J Med. 2024;391(7):585-597. doi:10.1056/NEJMoa2402614.
17. Saura C, Garcia-Saenz JA, Xu B, et al. Safety and efficacy of neratinib in combination with capecitabine in patients with metastatic human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2014;32(32):3626–33. doi: 10.1200/JCO.2014.56.3809.
18. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases: updated exploratory analysis of the HER2CLIMB. doi: 10.1001/jamaoncol.2022.5610.
19. Cagney DN, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro Oncol. 2017;19(11):1511–21. https://doi. org/10.1093/neuonc/nox077.
20. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial. Ann Oncol. 2020;31(10):1350-1358. doi:10.1016/j.annonc.2020.06.020.
21. Bartsch R, Berghoff AS, Furtner J, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. Nat Med. 2022;28(9):1840-1847. doi:10.1038/s41591-022-01935-8.
22. Hurvitz SA, Modi S, Li W, et al. 377O A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. Ann Oncology. 2023;34(2):335-336. doi: 10.1016/j.annonc.2023.09.554
23. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. Nat Med. Published online September 13, 2024. doi:10.1038/s41591-024-03261-7.
24. Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol. 2021;22(12):1692-1704. doi:10.1016/S1470-2045(21)00545-3.
25. Long GV, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018;19(5):672–81. doi: 10.1016/S1470-2045(18)30139-6.
26. Eroglu Z, Ribas A. Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy. Ther Adv Med Oncol. 2016;8(1):48–56. doi: 10.1177/ 1758834015616934.
27. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18(7):863-873. doi:10.1016/S1470-2045(17)30429-1.
28. Tawbi HA, Schadendorf D, Lipson EJ; RELATIVITY-047 Investigators. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022;386(1):24-34. doi: 10.1056/NEJMoa2109970.
29. Lebow ES, Pike LRG, Seidman AD, Moss N, Beal K, Yu Y. Symptomatic necrosis with antibody-drug conjugates and concurrent stereotactic radiotherapy for brain metastases. JAMA Oncol. 2023;9(12):1729-1733. doi:10.1001/jamaoncol.2023.4492.
30. Id Said B, Chen H, Jerzak KJ, et al. Trastuzumab emtansine increases the risk of stereotactic radiosurgery-induced radionecrosis in HER2 + breast cancer. J Neurooncol. 2022;159(1):177-183. doi:10.1007/s11060-022-04055-y.

31. Corbett K, Sharma A, Pond GR, et al. Central nervous system-specific outcomes of phase 3 randomized clinical trials in patients with advanced breast cancer, lung cancer, and melanoma. JAMA Oncol. 2021;7(7):1062-1064. doi:10.1001/jamaoncol.2021.1359.
32. Lazaratos AM, Petrecca K, Guiot MC, Jerzak KJ, Dankner M. CNS activity of trastuzumab deruxtecan in HER2-expressing non-small-cell lung cancer. Lancet Oncol. 2024;25(7):e282. doi:10.1016/S1470-2045(24)00261-4.
33. Sharma, A. E., Corbett, K., Soliman, H., Sahgal, A., Das, S., Lim-Fat, M. J., & Jerzak, K. J. (2023). Assessment of phase 3 randomized clinical trials including patients with leptomeningeal disease: A systematic review. JAMA oncol, 9(4), 566–567. doi: 10.1001/jamaoncol.2022.7364
34. Brastianos PK, Lee EQ, Cohen JV, et al. Single-arm, open-label phase 2 trial of pembrolizumab in patients with leptomeningeal carcinomatosis [published correction appears in Nat Med. 2020 Aug;26(8):1309. doi: 10.1038/s41591-020-0978-1]. Nat Med. 2020;26(8):1280-1284. doi:10.1038/s41591-020-0918-0.
35. Bartsch R, Jerzak KJ, Larrouquere L, Müller V, Le Rhun E. Pharmacotherapy for leptomeningeal disease in breast cancer. Cancer Treat Rev. 2024;122:102653. doi:10.1016/j.ctrv.2023.102653.
36. Khaled ML, Tarhini AA, Forsyth PA, Smalley I, Piña Y. Leptomeningeal disease (LMD) in patients with melanoma metastases. Cancers (Basel). 2023;15(6):1884. doi:10.3390/cancers15061884.
37. Wang Y, Yang X, Li NJ, Xue JX. Leptomeningeal metastases in non-small cell lung cancer: Diagnosis and treatment. Lung Cancer. 2022;174:1-13. doi:10.1016/j.lungcan.2022.09.013.
38. Park S, Baldry R, Jung HA, et al. Phase II Efficacy and Safety of 80 mg Osimertinib in Patients With Leptomeningeal Metastases Associated With Epidermal Growth Factor Receptor Mutation-Positive Non-Small Cell Lung Cancer (BLOSSOM). J Clin Oncol. 2024;42(23):2747-2756. doi:10.1200/JCO.24.00708.

About the Authors

Nathalie Baudoux, MD

Dr. Baudoux is currently a fellow and clinical instructor in gastrointestinal oncology at the Centre hospitalier de l'Université de Montréal (CHUM). She obtained her medical degree from the University of Tours (France) and then completed a residency in internal medicine and medical oncology in Switzerland.

Affiliations: Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC

Francine Aubin, MD, FRCPC

Dr. Francine Aubin received a medical degree from the Université de Montréal in 2002. She completed her residencies in internal medicine, hematology, and medical oncology at the same establishment. She is certified in all three specialties by the Royal College of Physicians and Surgeons of Canada. She specialized in gastrointestinal oncology during her fellowship at the BC Cancer Agency in Vancouver in 2009–2010. Dr. Aubin has been working as a hemato-oncologist since 2010 at the Centre hospitalier de l'Université de Montréal (CHUM). Her practice is mainly dedicated to treating gastrointestinal malignancies. She is actively involved in clinical research and contributes to a number of Phase I, II, and III studies. As a clinical associate professor at the Université de Montréal, she is actively engaged in education. She is the associate director of the Medical Oncology Training Program committee of the Université de Montréal. She is also in charge of the Medical Oncology Fellowship Program at the CHUM.

Affiliations: Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC

doi.org/10.58931/cot.2025.2133

The Role of Biomarkers in Upper Gastrointestinal Cancers

Nathalie Baudoux, MD
Francine Aubin, MD, FRCPC

Upper gastrointestinal (GI) cancers include esophageal, esophagogastric junction, and stomach cancers, which together represent the second leading cause of cancer-related mortality worldwide in both sexes, with approximately 1,100,000 deaths in 2022. The disease is usually diagnosed at an advanced non-curable stage, and conventional chemotherapy treatment is associated with poor prognosis. Advances have been made in the development of new therapies, including immunotherapy and targeted therapies. Biomarker identification has expanded treatment options and guides treatment selection. This article reviews the molecular characterization of GI cancers, which has been the subject of increasing research, and biomarker-targeted agents, representing a continually evolving landscape in upper GI cancers.

Introduction

Upper gastrointestinal (GI) cancers generally refer to malignancies of the esophagus, gastroesophageal junction (GEJ), and stomach. From a histological standpoint, GEJ and stomach cancers are usually adenocarcinomas, while squamous cell carcinomas (SCC) are most frequently located in the upper and middle parts of the esophagus. In Canada in 2023, stomach and esophageal cancer represented the 12th most common cancers in terms of incidence, with 6,800 new cases, and the 6th in terms of mortality, with 4,400 deaths.[1] Between 2010 and 2019, a study cohort from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER), showed an increase in the incidence of esophageal cancers in young people.[2] Most commonly, upper GI cancers are detected at an advanced stage for which treatment with curative intent is not possible. Over the years, advances have been made in the chemotherapy regimens for these types of cancers. Nevertheless, the prognosis remains poor, and a minority of patients will survive more than five years. More recently, promising new therapies have been developed, including immunotherapy and targeted therapies. The addition of these therapies to chemotherapy has improved outcomes for selected patients with upper GI cancers. The identification of biomarkers has expanded treatment options and is important to guide treatment selection.

A molecular classification has also emerged from molecular and genomic analysis of gastric cancer, as reported by The Cancer Genome Atlas (TCGA). Gastric adenocarcinomas can be categorized into four subtypes: tumors positive for Epstein-Barr virus (EBV), microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. Identifying these molecular subtypes and other biomarkers has allowed for a better understanding of the disease and the development of new targeted therapies.[3] In this article, we will discuss the role of the main biomarkers in upper GI cancers.

Biomarker Assessment

The multidisciplinary pan-Canadian expert working group recommends reflex testing for human epidermal growth factor 2 (HER2), mismatch repair (MMR) and/or microsatellite instability (MSI), claudin 18 isoform 2 (CLDN 18.2), and programmed cell death ligand 1 (PD-L1) in all patients at the time of diagnosis of gastric or GEJ adenocarcinoma.[4]

Immunohistochemistry (IHC) is a cost-effective method that uses antibodies to detect and localize specific antigens or proteins in cells or on the cell membrane. IHC is useful for the assessment of predictive and/or prognostic biomarkers, such as overexpression of transmembrane receptors involved in the activation of signaling pathways, such as human

epidermal growth factor 2 (HER2) and fibroblast growth factor receptor (FGFR). IHC is also used to determine the expression level of Claudin 18 isoform 2 (CLDN 18.2), a tight-junction molecule member of the claudin family. A cell surface protein that plays an essential role in immune checkpoint function, programmed cell death ligand 1 (PD-L1) can also be evaluated with IHC, as well as loss of mismatch repair (MMR) protein expression, which is also called MMR deficiency (dMMR).

IHC is the also the main method used for biomarker assessment in gastric or GEJ adenocarcinoma, preferentially on primary tumour specimens as done in clinical trials. In some cases, molecular testing must be performed to clarify IHC results. For example, when protein overexpression is equivocal, such as IHC 2+ for HER2, gene amplification of *HER2/neu* must be assessed by fluorescence in situ hybridization (FISH). Regarding MMR testing, some cases of heterogeneity in nuclear staining within the tumor may require further evaluation with polymerase chain reaction (PCR) to detect microsatellite instability (MSI).[5] Next-generation sequencing (NGS) in gastric and esophageal cancer is not recommended in standard clinical practice, as no actionable mutations have been identified yet.

Biomarker expression in esophageal and gastric cancers is heterogeneous, and variation within the primary tumor or between primary and metastatic sites can be observed, as well as temporal heterogeneity, due to the natural progression of the tumor or tumor evolution under treatment.[6]

The implementation of reflex predictive biomarker testing remains challenging as it requires sufficient laboratory personnel and pathologist resources; multidisciplinary collaboration involving pathologists is essential.

Biomarkers in Upper GI Cancers (*Table 1)*

HER2

HER2, encoded by the *ERBB2* (also known as *HER2/neu*) gene, was the first biomarker introduced into routine clinical practice for gastric and GEJ adenocarcinoma. It is a membrane receptor belonging to the epidermal growth factor receptor (EGFR) family of receptors and has intracellular tyrosine kinase activity, which is associated with growth and development. Two major mechanisms can lead to oncogenesis: mutation or amplification of *ERBB2*, of which the latter is generally correlated with overexpression of HER2. In gastric and GEJ adenocarcinomas, only HER2 amplification and/or overexpression is a predictive biomarker for HER2-targeted therapies, and is found in 10–20% of gastric and 30% of GEJ cancers, with intratumoral heterogeneity.[7] The randomized Phase 3 trial, TOGA, established the combination of trastuzumab, an anti-HER2 humanized monoclonal antibody, and chemotherapy as a new standard-of-care for first-line treatment in HER2-positive advanced gastric or GEJ cancers, by showing a statistically significant gain in overall survival (OS) over chemotherapy alone (13.8 vs. 11.1 months).[8] More recently, the randomized Phase 3 trial KEYNOTE-811 demonstrated a significant improvement in progression-free survival (PFS) (10 vs. 8.1 months) and OS (20 vs. 16.8 months), with the addition of pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, to trastuzumab plus chemotherapy, in the first-line treatment of HER2-positive advanced gastric or GEJ adenocarcinomas, with expression of PD-L1 (combined positive score [CPS] ≥1).[9] In subsequent-line therapy, including patients pre-treated with trastuzumab, trastuzumab deruxtecan, an antibody-drug conjugate, there was a significant improvement in overall response rate (ORR) (51% vs. 14%) and in OS (12.5 vs. 8.4 months) compared to physician choice of chemotherapy, in the DESTINY-Gastric01 randomized Phase 2 trial.[10] Because loss of HER2 expression after failure of trastuzumab-containing chemotherapy is now well described, it is recommended to consider biopsy at progression to evaluate changes in HER2 expression.

Unlike breast cancer, dual HER2 blockade with trastuzumab and pertuzumab (a humanized monoclonal antibody that inhibits the dimerization of HER2 with other HER2 family receptors) is not effective in HER2-positive gastric or GEJ cancers, nor at an advanced stage, as shown in the negative JACOB trial,[11] nor in the perioperative setting combined with FLOT chemotherapy (fluorouracil, leucovorin, oxaliplatin, and docetaxel), according to the results of the INNOVATION trial.[12]

PD-L1

PD-L1 expression is reported to be elevated in up to 40–65% of GEJ cancers. Two scoring methods of IHC data are used to assess PD-L1 expression in different types of cancer. The CPS evaluates the

	Prevalence	Testing	Treatment	Gain (primary endpoint in bold)	Trials / [references]
HER-2	Gastric: 10–20% GEJ: 30%	IHC If 2+: FISH	Trastuzumab + chemotherapy vs. placebo + chemotherapy	**mOS:** 13.8 vs. 11.1 months, *p=0.0046*	TOGA[8]
			PD-L1 CPS ≥1: Trastuzumab + chemotherapy + pembrolizumab vs. trastuzumab + chemotherapy + placebo	**mPFS S:** 10.0 vs. 8.1 months, *p=0.0002* **mOS:** 20.0 vs. 16.8 months, *p=0.004*	KEYNOTE-811[9]
PD-L1	40–65%, SCC >AC	IHC	AC Nivolumab + chemotherapy* vs. chemotherapy*	CPS ≥5: **mOS:** 14.4 vs. 11.1 months, *[HR: 0.7; 95% CI: 0.61-0.81]* **mPFS:** 13 vs 8 months, *[HR: 0.7; 95% CI: 0.6-0.81]*	CheckMate-649[16]
			Pembrolizumab + chemotherapy vs. chemotherapy*	PD-L1 CPS ≥10: **mOS:** 15.7 vs. 11.8 months, *[HR: 0.65; 95% CI: 0.53-0.79]* **mPFS:** 8.1 vs. 5.6 months, *[HR: 0.62; 95% CI: 0.51-0.76]*	KEYNOTE-859[17]
			SCC Pembrolizumab + cisplatin-5FU vs. cisplatin-5FU	PD-L1 CPS ≥10: **mOS:** 13.9 vs. 8.8 months, *p<0.0001* **mPFS:** 7.5 vs 5.5 months, *p<0.0001*	KEYNOTE-590[21] (SCC : 73.5%, AC 26.5% ; GEJ + oesophageal)
			nivolumab + FOLFOX vs. FOLFOX	PD-L1 TPS ≥1: **mOS:** 15.4 vs. 9.1 months, *p<0.001* **mPFS:** 6.9 vs. 4.4 months, *p=0.002*	CheckMate-648**[20]
			Ipilimumab-nivolumab vs. FOLFOX	**mOS:** 13.7 vs. 9.1 months, *p=0.001* **mPFS:** 4.0 vs. 4.4 months, *p=0.9*	

	Prevalence	Testing	Treatment	Gain (primary endpoint in bold)	Trials / [references]
dMMR	10%	IHC -If heterogeneity in nuclear staining: PCR for MSI assessment	<u>Advanced/metastatic:</u> Ipilimumab-nivolumab vs. chemotherapy*	**mOS:** NR vs. 10 months **ORR:** 70 vs. 57%	CheckMate-649 *(subgroup :44 patients)*[16]
			Nivolumab + chemotherapy* vs. chemotherapy*	**mOS:** 38.7 vs. 12.3 months **ORR:** 55 vs. 39 %	
			Pembrolizumab vs. chemotherapy (cisplatin + 5FU or capecitabine)	<u>PD-L1 CPS ≥1</u> **mOS:** NR vs. 8.5 months PD-L1 CPS ≥10 mOS NR vs. 13.6 months	KEYNOTE-062[26]
			<u>Early stage:</u> Ipilimumab + nivolumab/ surgery/nivolumab	59%: pCR 3 patients: cCR, no surgery	NEONIPINIGA *(Phase 2, 32 patients)*[25]
CLDN -18.2	30–40%	IHC	Zolbetuximab + FOLFOX vs. placebo + FOLFOX	**mPFS:** 11 vs. 8.9 months, *p=0.0024* **mOS:** 18.2 vs. 15.6 months, *p= 0.0075*	SPOTLIGHT[29]
			Zolbetuximab + CAPOX vs. placebo + CAPOX	**mPFS:** 8.2 vs. 6.8 months, *p=0.0007* **mOS:** 14.4 vs. 12.2 months, *p=0.118*	GLOW[30]
FGFR2b ***NOT APPROVED IN CANADA***	5–10%	IHC	Bemarituzumab + FOLFOX vs. placebo + FOLFOX	**mPFS:** 9.5 vs. 7.4 months, *p=0.073* **mOS:** 19.2 vs. 13.5 months *[HR: 0.77; 95% CI: 0.52-1.14]*	FIGHT[31]

Table 1. Prevalence, testing, and biomarker-based therapies in advanced upper GI cancers (*dMMR tumors: advanced and early stages*); *courtesy of Nathalie Baudoux, MD and Francine Aubin, MD, FRCPC.*

*FOLFOX or CAPOX
**open-label trial

Abbreviations: 5FU: fluorouracil, **AC:** adenocarcinoma, **CAPOX:** capecitabine and oxaliplatin, **cCR:** clinical complete response, **CI:** confidence interval, **CLDN 18.2:** claudin 18.2, **CPS:** combined positive score, **dMMR:** deficient mismatch repair, **FGFR2b:** fibroblast growth factor receptor 2b, **FISH:** fluorescence in situ hybridization, **FOLFOX:** folinic acid, fluorouracil, and oxaliplatin, **GEJ:** gastroesophageal junction, **GI:** gastrointestinal, **HER2:** human epidermal growth factor receptor 2, **HR:** hazard ratio, **IHC:** immunohistochemistry, **mOS:** median overall survival, **mPFS:** median progression-free survival, **MSI:** microsatellite instability, **NR:** not reached, **ORR:** overall response rate, **pCR:** pathological complete response, **PCR:** polymerase chain reaction, **PD-L1:** programmed cell death ligand 1, **SCC:** squamous cell carcinoma, **TPS:** tumor proportion score

number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) relative to all viable tumor cells, and the tumoral proportion score (TPS) evaluates the percentage of viable PD-L1-positive tumor cells. PD-L1 is well-known for its heterogeneity in the tumor and the tumor microenvironment, and expression may vary between the primary site and metastases, as well as before and after treatment.[13] CPS is used in gastric and GEJ adenocarcinomas, and a positive score predicts response to immunotherapy.[14,15] In the CheckMate 649 Phase 3 trial, patients with unresectable or metastatic gastric or GEJ adenocarcinomas were randomized to nivolumab plus chemotherapy (FOLFOX [folinic acid, fluorouracil, and oxaliplatin] or CAPOX [capecitabine and oxaliplatin) or chemotherapy alone. Improved OS was demonstrated for the entire population, but this effect was driven by the PD-L1 CPS ≥5 subgroup (14.4 vs. 11.1 months).[16] The efficacy subgroup analysis based on PD-L1 expression in this study showed limited OS benefit for the subgroup with PD-L1 CPS <5. In the KEYNOTE-859 trial, which included a similar population, pembrolizumab plus chemotherapy demonstrated a significant OS benefit over chemotherapy alone, particularly in the CPS ≥10 population (15.7 vs. 11.8 months).[17] The combination of immunotherapy and chemotherapy is now a standard treatment for eligible patients with gastric or GEJ adenocarcinomas with positive PD-L1 CPS, for which a benefit is mainly demonstrated for those with PD-L1 CPS 5.[18,19]

Therapies in advanced or metastatic esophageal SCC are also guided by PD-L1 expression, which is generally higher than in gastric and GEJ adenocarcinomas. The CheckMate 648 Phase 3 trial randomized patients with untreated, unresectable, or metastatic SCC to ipilimumab plus nivolumab, nivolumab plus chemotherapy, or chemotherapy alone. The two combination therapies had better OS than chemotherapy alone in all randomized populations; however, the patients with PD-L1 TPS ≥1 seemed to benefit more.[20] In the same setting, the Phase 3 trial KEYNOTE-590 demonstrated a gain in OS and PFS for pembrolizumab plus chemotherapy for patients with esophageal cancer, particularly in the CPS ≥10 subgroup.[21]

It has been demonstrated that EBV-positive tumors usually exhibit high levels of PD-L1 expression, which may partly explain the good response to immunotherapy in this tumor subtype.[22] While interesting, stronger data are needed before recommending EBV testing by EBV-encoded RNA in situ hybridization (EBER ISH) routinely in clinical practice.

dMMR/MSI-high

The role of the DNA MMR system is mainly to recognize and correct DNA mismatches generated during DNA replication. dMMR alters the length of repetitive DNA sequences, leading to high microsatellite instability (MSI-H). Loss of MMR proteins, such as MLH1, MSH2, MSH6, and PMS2, is associated with a germline mutation of one of several MMR genes found in Lynch syndrome or, most frequently, with hypermethylation of the *MLH1* promoter in sporadic tumors. Approximately 10% of gastric and GEJ adenocarcinomas are dMMR/MSI-H, and the incidence increases in patients older than 85 years.[23] MMR status has a prognostic and therapeutic impact on upper GI cancer, both in localized and in advanced stages. Indeed, a meta-analysis showed that patients diagnosed with operable GEJ cancer with MSI-H status do not benefit from perioperative chemotherapy with detrimental outcomes in OS and PFS.[24] Nevertheless, it is important to note that the chemotherapy regimen used in these trials did not include FLOT, which is now the standard of care for this indication. In patients with dMMR/MSI-H locally advanced resectable gastric/GEJ adenocarcinoma, NEONIPINIGA, a Phase 2 trial, evaluated the pathological complete response (pCR) rate after surgery and 12 weeks of neoadjuvant ipilimumab 1 mg/kg (2 doses) and nivolumab 240 mg (6 doses).[25] After surgery, upon the investigator's decision, patients received nine doses of adjuvant nivolumab. Of the 32 patients included, 29 had surgery and 17 had a pCR. Three patients did not have surgery due to complete radiological and endoscopic responses. Additional follow-up and data from other studies are needed to confirm the role of adjuvant perioperative immunotherapy. The INFINITY study (NCT04817826) investigates the

combination of durvalumab and tremelimumab as neoadjuvant definitive treatment in resectable gastric or GEJ MSI-H cancers. In advanced stages, data about the efficacy of immunotherapy for dMMR/MSI-H cancers are available from large Phase 3 trials previously discussed. In the first line setting, among 22 patients with dMMR/MSI-H tumors included in the CheckMate 649 trial, the combination of ipilimumab and nivolumab improved OS compared to chemotherapy (hazard ratio [HR]: 0.28; 95% confidence interval [CI]: 0.08–0.92).[16] Finally, an exploratory analysis of one Phase 2 (KEYNOTE-059) and two Phase 3 (KEYNOTE-061, KEYNOTE-062) studies indicated better outcomes in terms of ORR, PFS, and OS for those treated with pembrolizumab alone or pembrolizumab plus chemotherapy, compared to chemotherapy alone, regardless of the line of therapy in which it was received.[26]

CLDN 18.2

The CLDNs are a family of tight junction transmembrane proteins that play an important role in regulating tissue permeability, paracellular transport, and signal transduction. CLDN 18.2 is an isoform of CLDN and is mainly expressed in normal gastric tissues.[27] During malignant transformation, alteration in cell polarity and particularly the disruption of tight junctions leads to exposure of the CLDN 18.2 epitope, making it accessible for targeting treatments such as monoclonal antibodies. CLDN 18.2 positivity among metastatic gastric cancers is about 30–40%.[28] Zolbetuximab, a chimeric monoclonal antibody that targets CLDN 18.2 with antitumor activity induced through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), has been evaluated in two Phase 3 trials in combination with standard chemotherapy. The first study, SPOTLIGHT, included previously untreated patients with CLDN 18.2+ unresectable or metastatic gastric or GEJ adenocarcinomas. Patients were randomized between mFOLFOX6 plus zolbetuximab versus mFOLFOX plus placebo. The addition of zolbetuximab to mFOLFOX was associated with a statistically significant improvement in PFS (11 vs. 8.9 months) and OS (18.2 vs. 15.6 months).[29] In the second trial, GLOW, patients were randomized to CAPOX plus zolbetuximab versus CAPOX plus placebo.[30] A statistically significant gain in PFS (8.2 vs. 6.8 months) and OS (14.4 vs. 12.2 months) was shown with the addition of zolbetuximab. A combined analysis of these two trials confirmed a statistically significant gain in OS (16.4 vs. 13.7 months) and PFS (9.2 vs. 8.2 months).[31] Zolbetuximab represents a new first-line therapy for patients with CLDN 18.2+ tumors. Nevertheless, the best standard treatment is not well established for patients with overlapping expression of PD-L1 and CLDN 18.2. Future studies will be required to determine the best therapy for this subpopulation.

FGFR2b

FGFR are a family of transmembrane tyrosine kinase receptors involved in activating signaling pathways responsible for cell proliferation, survival, angiogenesis, and migration (metastasis). The most common alteration is FGFR2b amplification, which results in FGFR2 protein overexpression, and occurs in MMR-proficient tumors, which are generally without PD-L1 expression or HER2 amplifications.[32] This subtype represents approximately 5–10% of gastric cancers and is associated with poor outcomes.[33] FGFR2 overexpression, which can occur without gene amplification in cases of epigenetic changes, occurs in ranges between 30% and 60% of all gastric cancers. The randomized Phase 2 FIGHT trial explored the efficacy and safety of bemarituzumab, a humanized monoclonal antibody specific to FGFR2b.[34] Patients with untreated advanced gastric or GEJ adenocarcinomas with FGFR2b overexpression and/or FGFR2 gene amplification were randomized to the combination of mFOLFOX6 plus bemarituzumab or mFOLFOX6 plus placebo. The combination therapy showed a numerically but not statistically significant longer median PFS (9.5 vs. 7.4 months) and OS (19.2 vs. 13.5 months) than chemotherapy alone, and efficacy was more pronounced in those with FGFR2b overexpression in ≥10% of tumor cells. The Phase 3 FORTITUDE-102 study is ongoing to determine if bemarituzumab could be a new treatment option in combination with chemotherapy and immunotherapy.

Conclusion

Upper GI cancers represent a heterogenous disease that is mostly diagnosed at an advanced stage and is associated with a poor prognosis with conventional treatments. The identification of biomarkers has led to the development of new therapies. Biomarkers are also useful to predict which patients will benefit from immunotherapy. These predictive biomarkers are important to select the best treatment approach for each patient, allowing personalized treatment strategies. Patients with advanced esophagogastric adenocarcinoma should have their tumor tested for MMR status, and HER2, PD-L1, and CLDN 18.2 expression at first diagnosis. The utility of other emerging biomarkers, such as FGFR2b overexpression or MET gene alterations, is currently investigated in clinical trials.[35] Further progress in biomarker research is essential to shape the landscape of personalized therapies in oncology.

Correspondence

Francine Aubin, MD, FRCPC
Email: francine.aubin.med@ssss.gouv.qc.ca

Financial Disclosures

N.B.: None declared.
F.A.: Consulting/Advisory: Taiho Pharmaceutical, Pfizer, Merck, Bristol-Myers Squibb (Canada), Incyte Biosciences (Canada), Amgen, Astellas, AstraZeneca **Canada; Speaker's Bureau:** Taiho Pharmaceutical, Merck, Amgen, Bristol-Myers Squibb (Canada), AstraZeneca Canada, Incyte;
Institutional Research Funding: Bristol-Myers Squibb/Medarex, GSK, Merck, Novartis

References

1. https://cancer.ca/statistiques
2. Koh B, Tan DJH, Ng CH, Fu CE, Lim WH, Zeng RW, et al. Patterns in Cancer Incidence Among People Younger Than 50 Years in the US, 2010 to 2019. JAMA Netw Open. 2023;6(8):e2328171. doi: 10.1001/jamanetworkopen.2023.28171.
3. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202-9. doi: 10.1038/nature13480.
4. Brezden-Masley C, Fiset PO, Cheung CC, Arnasson T, Bateman J, Borduas M, Evaristo G, Ionescu DN, Lim HJ, Sheffield BS, Soldera SV, Streukler CJ, ,Canadian Consensus Recommendations for Predictive Biomarker Testing in Gastric and Gastroesophageal Junction Adenocarcinoma, Current Oncology 2024, 31(12), 7770-7786, https://doi.org/10.3390/curroncol31120572
5. Zito Marino F, Amato M, Ronchi A, Panarese I, Ferraraccio F, De Vita F, et al. Microsatellite Status Detection in Gastrointestinal Cancers: PCR/NGS Is Mandatory in Negative/Patchy MMR Immunohistochemistry. Cancers (Basel). 2022;14(9):2204. doi:10.3390/cancers14092204.
6. Lee HS. Spatial and Temporal Tumor Heterogeneity in Gastric Cancer: Discordance of Predictive Biomarkers. J Gastric Cancer. 2025;25(1):192-209. doi: 10.5230/jgc.2025.25.e3.
7. Grillo F, Fassan M, Sarocchi F, Fiocca R, Mastracci L. HER2 heterogeneity in gastric/gastroesophageal cancers: From benchside to practice. World J Gastroenterol. 2016 Jul 14;22(26):5879-87. doi: 10.3748/wjg.v22.i26.5879.
8. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97. doi: 10.1016/S0140-6736(10)61121-X. Erratum in: Lancet. 2010;376(9749):1302.
9. Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, et al. KEYNOTE-811 Investigators. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet. 2023;402(10418):2197-2208. doi: 10.1016/S0140-6736(23)02033-0.

10. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020;382(25):2419-2430. doi: 10.1056/NEJMoa2004413.
11. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Siddiqui A, et al. Pertuzumab, trastuzumab, and chemotherapy in HER2-positive gastric/gastroesophageal junction cancer: end-of-study analysis of the JACOB phase III randomized clinical trial. Gastric Cancer. 2023;26(1):123-131. doi: 10.1007/s10120-022-01335-4.
12. Wagner AD, Grabsch HI, Mauer M, Marreaud S, Caballero C, Thuss-Patience P, et al. Integration of trastuzumab (T), with or without pertuzumab (P), into perioperative chemotherapy (CT) of HER-2 positive gastric (GC) and esophagogastric junction cancer (EGJC): First results of the EORTC 1203 INNOVATION study, in collaboration with the Korean Cancer Study Group, and the Dutch Upper GI Cancer group, J Clin Oncol. 2023;41(16):suppl 4057. doi: 10.1200/JCO.2023.41.16.
13. Zhou KI, Peterson B, Serritella A, Thomas J, Reizine N, Moya S, et al. Spatial and Temporal Heterogeneity of PD-L1 Expression and Tumor Mutational Burden in Gastroesophageal Adenocarcinoma at Baseline Diagnosis and after Chemotherapy. Clin Cancer Res. 2020;26(24):6453-6463. doi: 10.1158/1078-0432.CCR-20-2085.
14. Lian J, Zhang G, Zhang Y, Liu H, Zhang J, Nan P, et al. PD-L1 and HER2 expression in gastric adenocarcinoma and their prognostic significance. Dig Liver Dis. 2022;54(10):1419-1427. doi: 10.1016/j.dld.2022.01.128.
15. Yoon HH, Jin Z, Kour O, Kankeu Fonkoua LA, Shitara K, Gibson MK, et al. Association of PD-L1 Expression and Other Variables With Benefit From Immune Checkpoint Inhibition in Advanced Gastroesophageal Cancer: Systematic Review and Meta-analysis of 17 Phase 3 Randomized Clinical Trials. JAMA Oncol. 2022;8(10):1456-1465. doi: 10.1001/jamaoncol.2022.3707.
16. Janjigian YY, Ajani JA, Moehler M, Shen L, Garrido M, Gallardo C, et al. First-Line Nivolumab Plus Chemotherapy for Advanced Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma: 3-Year Follow-Up of the Phase III CheckMate 649 Trial. J Clin Oncol. 2024;42(17):2012-2020. doi: 10.1200/JCO.23.01601.
17. Rha SY, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, et al. KEYNOTE-859 investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24(11):1181-1195. doi: 10.1016/S1470-2045(23)00515-6.. Erratum in: Lancet Oncol. 2024;25(12):e626. doi: 10.1016/S1470-2045(24)00650-8.
18. Formica V, Morelli C, Fornaro L, Riondino S, Rofei M, Fontana E, et al. PD-L1 threshold predict efficacy of immune checkpoint inhibition in first-line treatment of advanced gastroesophageal adenocarcinoma. A systematic review and meta-analysis of seven phase III randomized trials. ESMO open. 2024;9(11):103937.
19. Rajdev L, Kennedy E.B, Shah M.A. Immunotherapy and targeted therapy for advanced gastroesophageal cancer: ASCO Guideline Q and A. J Clin Oncol. 2023;19(4). doi: 10.1200/OP.22.00818
20. Doki Y, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, et al. CheckMate 648 Trial Investigators. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022;386(5):449-462. doi: 10.1056/NEJMoa2111380.
21. Sun JM, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, et al. KEYNOTE-590 Investigators. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. 2021 ;398(10302):759-771. doi: 10.1016/S0140-6736(21)01234-4. Erratum in: Lancet. 2021;20;398(10314):1874. doi: 10.1016/S0140-6736(21)02487-9.
22. Salnikov MY, MacNeil KM, Mymryk JS. The viral etiology of EBV-associated gastric cancers contributes to their unique pathology, clinical outcomes, treatment responses and immune landscape. Front Immunol. 2024;15:1358511. doi: 10.3389/fimmu.2024.1358511.
23. Polom K, Marrelli D, Roviello G, Pascale V, Voglino C, Rho H, et al. Molecular key to understand the gastric cancer biology in elderly patients-The role of microsatellite instability. J Surg Oncol. 2017;115(3):344-350. doi: 10.1002/jso.24513.
24. Pietrantonio F, Miceli R, Raimondi A, Kim YW, Kang WK, Langley RE, et al. Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer. J Clin Oncol. 2019;37(35):3392-3400. doi: 10.1200/JCO.19.01124.

25. André T, Tougeron D, Piessen G, de la Fouchardière C, Louvet C, Adenis A, et al. Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability-High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. J Clin Oncol. 2023;41(2):255-265. doi: 10.1200/JCO.22.00686.
26. Chao J, Fuchs CS, Shitara K, Tabernero J, Muro K, Van Cutsem E, et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability–High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA Oncology. 2021;7(6):895. https://doi.org/10.1001/jamaoncol.2021.0275.
27. Chen J, Xu Z, Hu C, Zhang S, Zi M, Yuan L, et al. Targeting CLDN18.2 in cancers of the gastrointestinal tract: New drugs and new indications. Front Oncol. 2023;13:1132319. doi: 10.3389/fonc.2023.1132319.
28. Klempner SJ, Janjigian YY, Wainberg ZA. Claudin18. who? Examining biomarker overlap and outcomes in claudin18.2-positive gastroesophageal adenocarcinomas. ESMO Open. 2023;8(2):100778. doi: 10.1016/j.esmoop.2022.100778.
29. Shitara K, Van Cutsem E, Lordick F, Enzinger PC, Ilson DH, Shah MA, et al. Final Overall Survival Results from Phase 3 SPOTLIGHT Study Evaluating Zolbetuximab + mFOLFOX6 as First-Line (1L) Treatment for Patients (Pts) with Claudin 18 Isoform 2 (CLDN18.2)+, HER2−, Locally Advanced (LA) Unresectable or Metastatic Gastric or Gastroesophageal Junction (mG/GEJ) Adenocarcinoma. J Clin Oncol. 2024;42,(16_suppl):4036–4036. doi: 10.1200/JCO.2024.42.16_suppl.4036.
30. Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023;29(8):2133-2141. doi: 10.1038/s41591-023-02465-7.
31. Shitara K, Shah MA, Lordick F, Van Cutsem E, Ilson DH, Klempner SJ, et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma. N Engl J Med. 2024;391(12):1159-1162. doi: 10.1056/NEJMc2409512.
32. Su, X., Zhan, P., Gavine, P. et al. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study. Br J Cancer. 2015;110:967–975. doi: 10.1038/bjc.2013.802
33. Lau DK, Collin JP, Mariadason JM. Clinical Developments and Challenges in Treating FGFR2-Driven Gastric Cancer. Biomedicines. 2024;12(5):1117. doi: 10.3390/biomedicines12051117.
34. Wainberg ZA, Kang YK, Lee KW, Qin S, Yamaguchi K, Kim IH, et al. Bemarituzumab as first-line treatment for locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma: final analysis of the randomized phase 2 FIGHT trial. Gastric Cancer. 2024;27(3):558-570. doi: 10.1007/s10120-024-01466-w.
35. Zhang Y, Shen L, Peng Z. Advances in MET tyrosine kinase inhibitors in gastric cancer. Cancer Biol Med. 2024;21(6):484–98. doi: 10.20892/j.issn.2095-3941.2024.0044.

About the Authors

Samitha Andrahennadi, MD

Dr. Samitha Andrahennadi is an internal medicine resident at the University of Saskatchewan. Throughout undergraduate training and medical school, Samitha sought out research experiences in cancer and oncology. He hopes to complete the next step in his training as a medical oncology fellow.

Affiliations: Internal Medicine, College of Medicine, University of Saskatchewan

Mita Manna, MD, FRCPC

Dr. Mita Manna is a Medical Oncologist at the Saskatoon Cancer Centre, Saskatoon, Saskatchewan, and Assistant Professor within the Department of Oncology, University of Saskatchewan. She is the Provincial Disease Site Lead for Breast Malignancies and a Nucleus Member for the REAL Alliance Breast Cancer Canada (Research Excellence and Active Leadership). Her research interests include quality improvement and real-world evidence. She is also actively involved in medical education.

Affiliations: Medical Oncologist, Saskatoon Cancer Centre, Saskatchewan Cancer Agency
Assistant Professor, Department of Oncology, University of Saskatchewan

doi.org/10.58931/cot.2025.2134

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

Samitha Andrahennadi, MD
Mita Manna, MD, FRCPC

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.

Correspondence

Mita Manna, MD, FRCPC
Email: Mita.Manna@saskcancer.ca

Financial Disclosures

S.A.: None declared.
M.M.: Speaker honoraria: AstraZeneca, Gilead Sciences, Merck, Pfizer, Eli Lilly, Novartis, Knight Therapeutics, Daichii-Sankyo, and Seagen;
Consulting Fees: Gilead Sciences, Eli Lilly, Novartis, Merck, Pfizer, Daichii-Sankyo, AstraZeneca, Roche, and Seagen;
Grants/Research support: AstraZeneca, RUH Women Leading Philanthropy

References

1. Brenner DR, Poirier A, Woods RR, Ellison LF, Billette JM, Demers AA, et al. Projected estimates of cancer in Canada in 2022. CMAJ. 2022 May 2;194(17):E601–7.
2. Bekes I, Huober J. Extended Adjuvant Endocrine Therapy in Early Breast Cancer Patients—Review and Perspectives. Cancers. 2023 Aug 21;15(16):4190.
3. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111–21.
4. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021 Dec 16;385(25):2336–47.
5. Prat A, Guarneri V, Pascual T, Brasó-Maristany F, Sanfeliu E, Paré L, et al. Development and validation of the new HER2DX assay for predicting pathological response and survival outcome in early-stage HER2-positive breast cancer. EBioMedicine. 2022 Jan;75:103801.
6. Sparano JA, Crager MR, Tang G, Gray RJ, Stemmer SM, Shak S. Development and Validation of a Tool Integrating the 21-Gene Recurrence Score and Clinical-Pathological Features to Individualize Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer. J Clin Oncol. 2021 Feb 20;39(6):557–64.
7. Slamon D, Lipatov O, Nowecki Z, McAndrew N, Kukielka-Budny B, Stroyakovskiy D, et al. Ribociclib plus Endocrine Therapy in Early Breast Cancer. N Engl J Med. 2024 Mar 21;390(12):1080–91.
8. Hortobagyi GN, Lacko A, Sohn J, Cruz F, Ruiz Borrego M, Manikhas A, et al. A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial. Ann of Oncol. 2024 Oct;S092375342404064X.
9. Rastogi P, O'Shaughnessy J, Martin M, Boyle F, Cortes J, Rugo HS, et al. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. J Clin Oncol. 2024 Mar 20;42(9):987–93.
10. Gnant M, Dueck AC, Frantal S, Martin M, Burstein HJ, Greil R, et al. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2022 Jan 20;40(3):282–93.
11. Loibl S, Marmé F, Martin M, Untch M, Bonnefoi H, Kim SB, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer—The Penelope-B Trial. J Clin Oncol. 2021 May 10;39(14):1518–30.
12. Rugo HS, O'Shaughnessy J, Boyle F, Toi M, Broom R, Blancas I, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. Ann Oncol. 2022 Jun;33(6):616–2.
13. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1 - or BRCA2 -Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394–405.
14. Garber J. GS1-09: OlympiA—Phase 3, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1 and/or BRCA2 pathogenic variants and high risk HER2-negative primary breast cancer: longer term follow-up. Presented at: San Antonio Breast Cancer Symposium; 2024 Dec 10-13; San Antonio, TX.
15. Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. JNCC. 2021 Jan 6;19(1):77–102.
16. Geyer CE, Untch M, Huang CS, Mano MS, Mamounas EP, Wolmark N, et al. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. N Engl J Med. 2025 Jan 15;392(3):249–57.
17. Loibl S, Jassem J, Sonnenblick A, Parlier D, Winer E, Bergh J, et al. Adjuvant Pertuzumab and Trastuzumab in Early Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer in the APHINITY Trial: Third Interim Overall Survival Analysis With Efficacy Update. J Clin Oncol. 2024 Nov;42(31):3643–51.
18. Chan A, Moy B, Mansi J, Ejlertsen B, Holmes FA, Chia S, et al. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2021 Feb;21(1):80-91.e7.

19. O'Sullivan CC, Ballman KV, McCall L, Kommalapati A, Zemla T, Weiss A, et al. Alliance A011801 (compassHER2 RD): Postneoadjuvant T-DM1 + Tucatinib/Placebo in Patients with Residual HER2-Positive Invasive Breast Cancer. Future Oncol. 2021 Dec;17(34):4665–76.
20. Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. The Lancet. 2023 Jan;401(10371):105–17.
21. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810–21.
22. Schmid P, Cortes J, Dent R, McArthur H, Pusztai L, Kümmel S, et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. N Engl J Med. 2024 Nov 28;391(21):1981–91.
23. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun;376(22):2147–59.
24. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 Apr 22;384(16):1529–41.
25. Lipsyc-Sharf M, De Bruin EC, Santos K, McEwen R, Stetson D, Patel A, et al. Circulating Tumor DNA and Late Recurrence in High-Risk Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Breast Cancer. J Clin Oncol. 2022 Aug 1;40(22):2408–19.
26. Turner NC, Swift C, Jenkins B, Kilburn L, Coakley M, Beaney M, et al. Results of the c-TRAK TN trial: a clinical trial utilising ctDNA mutation tracking to detect molecular residual disease and trigger intervention in patients with moderate- and high-risk early-stage triple-negative breast cancer. Ann Oncol. 2023 Feb;34(2):200–11.

Canadian Oncology Today
Science for the Real World

canadianoncologytoday.com

Canadian Oncology Today is published three times per year in English and in French (ISSN 2818-1131) under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) license by Catalytic Health in Toronto, Ontario, Canada.

Register for future digital and print issues by visiting us at catalytichealth.com/cot

Looking for more?
All back issues are available online at canadianoncologytoday.com