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Table of Contents

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About the Authors

Ronan A. McLaughlin, MD

Dr. Ronan McLaughlin is an Irish trained fellow working with Dr. Elimova and the gastrointestinal medical oncology team at the Princess Margaret Cancer Centre (2023-2025).

Affiliations: Princess Margaret Cancer Centre, University Health Network, University of Toronto, Canada

Elena Elimova, MD

Dr. Elena Elimova is Assistant Professor of Medicine at the University of Toronto and Adjunct Assistant Professor GI Medical Oncology at MD Anderson Cancer Center. She holds the position of Co-Chair Esophago-Gastric Disease Oriented Group Canadian Clinical Trials Group and is a Staff Medical Oncologist at Princess Margaret Cancer Centre.

Affiliations: Princess Margaret Cancer Centre, University Health Network, University of Toronto, Canada

Current and Emerging Treatment Options for HER2-Positive Gastroesophageal Cancer

Ronan A. McLaughlin, MD
Elena Elimova, MD

Gastroesophageal Cancer and HER2 Biology:

Gastroesophageal cancer (GEC) is the fifth most common cancer and the second most common cause of cancer-related mortality, with 1.3 million annual deaths worldwide.[1,2] The global incidence is increasing, particularly among younger patients.[3] GEC can be classified into subtypes based on anatomic location, histology, molecular characteristics, or tumour biology and genomics.[4] In approximately 20% of all GECs overexpression of HER2 is identified.[5] The landscape of treatment options in this patient population is evolving rapidly. This review summarizes the progress of HER2-directed therapies for advanced disease and highlights future directions in targeting the disease.

The epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinase receptors, EGFR/HER1, HER2/neu, HER3, and HER4, all have an extracellular ligand-binding domain, lipophilic transmembrane domain, and an intracellular domain with tyrosine kinase activity[6], binding to these receptors results in activation of downstream RAS/MAPK and PI3K/AKT pathways.[6-8] In turn, this induces cell proliferation, differentiation, migration, and survival. The phase III Trastuzumab for Gastric Cancer (ToGA) trial reported the incidence of HER2-positive gastric cancer to be 22%.[9] Therefore, targeting HER2 and its downstream signaling pathways holds important potential as a therapeutic strategy. **Figure 1** illustrates potential targeting mechanisms that will be discussed in this review.

In GEC, HER2 positivity is distinct from that in other tumour types, such as breast cancer, as it demonstrates more heterogeneous HER2 immunohistochemistry (IHC) staining patterns and lower HER2 expression.[10] In HER2-positive breast cancer, combination blockade and sequential HER2 targeting at progression has revolutionized the treatment.[11] However, similar methods with the same therapies have not shown to have the same benefit in GEC.[12]

HER2-targeted Therapy in Metastatic Disease; The Current Landscape and Future Directions

Trastuzumab, a monoclonal anti-HER2 antibody, binds to the extracellular domain of HER2, inhibits its downstream signaling, and promotes antibody-dependent cellular cytotoxicity (ADCC).[9] In 2010, the ToGA study established trastuzumab as the standard treatment for first-line, metastatic GEC. It was a landmark study and was the first to demonstrate an improvement in overall survival (OS) (13.8 vs. 11.1 months).[9] In a preplanned exploratory analysis of patients with high HER2 expression in the tumours, defined as IHC 3+ or IHC 2+/FISH-positive—which has subsequently become the diagnostic criteria—the survival benefit was higher (16.0 vs. 11.8 months).[9]

Emerging preclinical and clinical evidence have confirmed the efficacy of dual anti-PD-1 and HER2-blockade, and phase II studies investigating these therapies have demonstrated an impressive objective response rate (ORR) of 91%.[13,14] The ToGA study, as a historical control, had an ORR of 47%[9]. Furthermore, the combination therapy showed a median progression-free survival (PFS) and OS of 13.0 and 27.0 months, respectively.[14] The mechanism of action of the interaction between HER2 and PD-1 inhibitors is not fully understood. It is thought to be a consequence of trastuzumab enhancing HER2 internalization and cross-presentation by dendritic cells, stimulating HER2-specific T-cell responses.[15] The stimulation of T cell responses results in the upregulation of PD-1 expression on tumour-infiltrating lymphocytes and expression

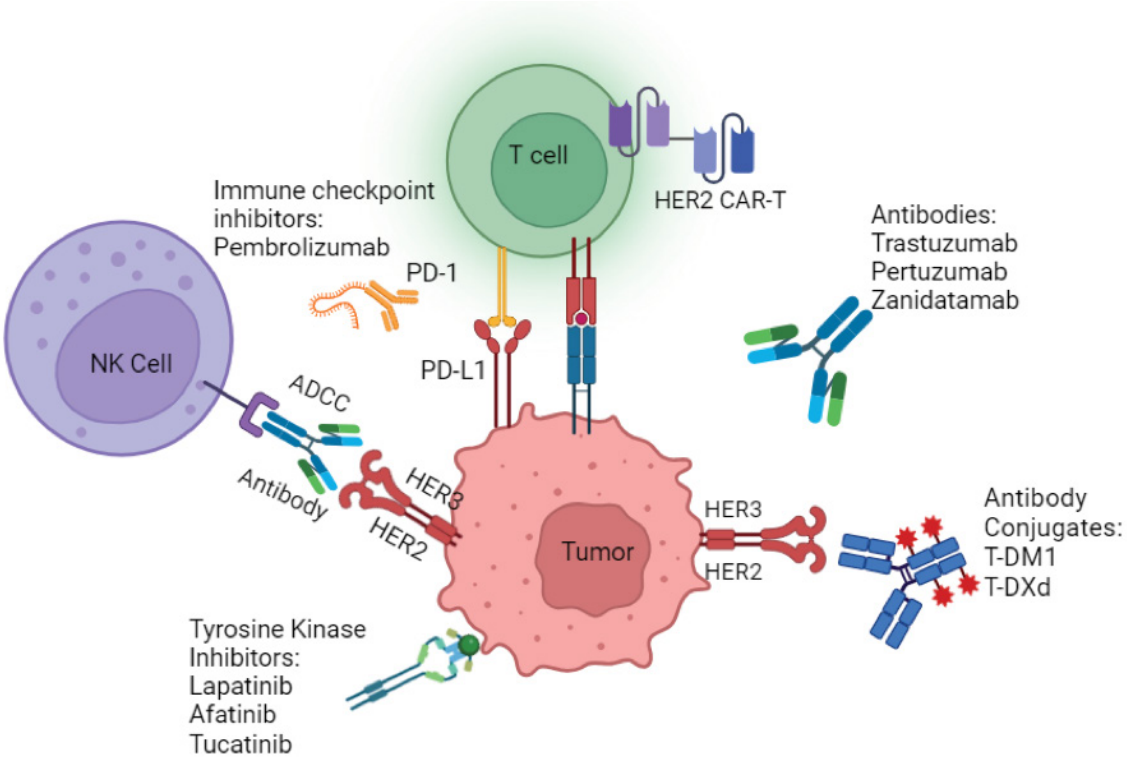

Figure 1. Strategies for targeting HER2 positive; *courtesy of Ronan Andrew McLaughlin, MD and Elena Elimova, MD*

Anti-HER2 antibodies include trastuzumab, pertuzumab, and zanidatamab. Antibody-drug conjugates include T-DM1 and T-DXd. Tyrosine kinase inhibitors include lapatinib, afatinib, and tucatinib. Receptors on NK cells bind to the anti-HER2 antibodies bound to HER2 on tumour cells and trigger an anti-tumour immune response via ADCC. Immune checkpoint inhibitors, including pembrolizumab, target co-inhibitory signals for T cell antigen receptor signalling (e.g PD-1 or PD-L1) to enhance T cell anti-tumour immunity. CAR-T cells expressing HER2-specific CARs may serve as a future treatment option for HER2-positive GEC. **Abbreviations: ADCC:** antibody-dependent cellular cytotoxicity; **CAR:** chimeric antigen receptor; **GEC:** gastroesophageal cancer; **NK:** natural killer; **PD-1:** programmed cell death protein 1; **PD-L1:** programmed cell death ligand 1; **T-DXd:** trastuzumab deruxtecan; **T-DM1:** ado-trastuzumab emtansine.

of PD-L1 in the tumour microenvironment, and by blocking PD-1, pembrolizumab can increase the efficacy of the therapy.[15] In the subsequent, randomised, global phase III KEYNOTE-811 trial, the addition of pembrolizumab to trastuzumab and chemotherapy led to a 23% improvement in ORR (74.4% vs. 51.9%).[16] It must be noted that there was a significant difference in the inclusion of patients with IHC 3+ disease in KEYNOTE 811 versus ToGA, (82% vs. 48% in the treatment arm with similar differences in the control), which may explain the significant differences observed in ORR. The PFS was longer in the pembrolizumab group than in the placebo group at the third interim analysis (median 10.0 months vs. 8.1 months; HR: 0.73). In the subgroup of patients with tumours with a PD-L1 combined positive score (CPS) of ≥1, the PFS was 10.9 months in response to treatment (vs. 7.3 months for placebo; HR: 0.71), but did not differ in the population with a PD-L1 CPS of <1 (median 9.5 months vs. 9.5 months; HR 1·03). PFS was consistently improved with pembrolizumab versus placebo irrespective of disease burden, number of metastatic sites, or patient performance status, with the exception of patients with tumours with a PD-L1 CPS of <1.[17]

Trial	Setting	Design	Outcomes
ToGA	First-Line Metastatic	Chemotherapy +/- Trastuzumab	Median OS 13.8 vs. 11.1 months
KEYNOTE-811	First-Line Metastatic	Trastuzumab + Chemotherapy +/- Pembrolizumab	ORR 74% vs. 52% CR 11% vs. 3%
DESTINY-Gastric 01	Third-Line Metastatic (Asian patients)	T-DXd vs. physicians' choice of taxane or irinotecan	ORR 51% vs. 14% Median PFS: 5.6 vs. 3.5 months Median OS: 12.5 vs. 6.4 months
DESTINY-Gastric 02	Second-Line Metastatic (Western patients)	T-DXd	ORR: 42% Median PFS: 5.6 months Median OS: 12.1 months

Table 1. Landmark studies that have changed the landscape of metastatic HER2 positive GEC treatment; *courtesy of Ronan Andrew McLaughlin, MD and Elena Elimova, MD*

Abbreviations: CR: complete response; **ORR:** objective response rate; **OS:** overall survival; **PFS:** progression-free survival; **T-DXd:** trastuzumab deruxtecan.

At the same third interim analysis, median OS was 20.0 months in the pembrolizumab group versus 16.8 months in the placebo group (HR: 0.84), and 20.0 months versus 15.7 months (HR: 0.81) in the population with a PD-L1 CPS of ≥1.[17] These results led to the FDA approval of pembrolizumab with trastuzumab and chemotherapy as a new standard-of-care in the first-line setting, initially approved in all patients, but this was later updated to patients with a CPS ≥1 (**Table 1**), subsequently leading to Health Canada and European Medicines Agency approvals.[17]

Several other first-line studies in metastatic HER2-positive GEC have not resulted in better outcomes. The TyTAN and LOGiC trials investigated lapatinib, a reversible TKI that binds to the intracellular ATP-binding domains of HER2 and EGFR, with disappointing results.[18,19] Additionally, the JACOB trial of dual HER2 blockade, in which trastuzumab and chemotherapy were combined with pertuzumab, a monoclonal anti-HER2 antibody, was also unsuccessful in showing survival benefits.[12] Archival tissue HER2 assessment for assessing eligibility was permitted in all three studies, and the TyTAN and LOGIC studies permitted local HER2 status assessments.[18,19] This may have influenced the results based on research results on the development of resistance to HER2. While TKI have not yet been successful in HER2-positive GEC, tucatinib, a reversible HER2-targeted small-molecule TKI, is currently under investigation. Tucatinib plus trastuzumab has shown tumour growth inhibition in HER2-positive gastric cancer (GC) xenograft models and a phase Ib/II trial in which tucatinib is combined with trastuzumab and chemotherapy for untreated advanced GC is ongoing (NCT04430738). The phase II/III MOUNTAINEER 02 study, which was designed to test the efficacy of tucatinib when combined with trastuzumab, paclitaxel, and ramucirumab in the second-line of treatment, has stopped enrolling patients (NCT04499924).[20] The reasons for this are unclear.

Although the therapies assessed by ToGA and KEYNOTE 811 have improved outcomes through several mechanisms, most patients ultimately develop resistance.[9,17] Due to the heterogeneity of GEC, if HER2-positive clones are successfully eradicated with HER2 inhibition,

HER2-negative clones can drive resistance.[21] HER2 loss is one of the primary causes of acquired resistance to trastuzumab.[22] In patients with HER2-positive gastric cancer receiving trastuzumab, 29%–64% developed loss of HER2 expression during treatment (IHC score <3+ and absence of ISH amplification) and/or loss of HER2 overexpression (IHC "down scoring" from 2+/3+ to 0/1+).[23] At the same time, the heterogeneity of HER2 gene expression increased. This phenomenon was found more frequent in tumours with an initial IHC score of 2+, suggesting that HER2 status needs to be reassessed before starting second-line anti-HER2 therapy.[23] In the event a repeat tissue biopsy is not easily obtained, there is evidence to support the use of liquid biopsy to confirm HER2 status. Studies have determined the HER2 amplification status from circulating DNA fragments in blood using a HER2 Copy Number Variation assay to establish a minimally invasive approach. Furthermore and most importantly, changes in HER2 status during therapy have been confirmed in liquid biopsies, indicating that it reflects the changes in HER2 status and may aid in assessing therapy efficiency and uncovering treatment resistance.[24] Unfortunately, several second-line studies allowed for inclusion based on archival tissue, which may have impacted their results.

Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC) consisting of a monoclonal anti-HER2 antibody bound by a cleavable tetrapeptide-based linker to a cytotoxic topoisomerase I inhibitor payload, has transformed options in trastuzumab-refractory disease. With a drug-to-antibody ratio of 8-to-1, the released payload diffuses across cellular membranes, entering neighboring tumour cells. Given the biological heterogeneity of GEC, this high drug-to-antibody ratio and the membrane permeability of its payload have resulted in significant success.[25] The DESTINY-Gastric01 study evaluated T-DXd as third or later line treatment. This open-label phase II trial, which required repeat biopsy to confirm HER2-positivity, demonstrated superior efficacy of T-DXd compared with the physician's choice of paclitaxel or irinotecan, with an improved ORR (51% vs. 14%), median PFS (5.6 vs. 3.5 months), and OS (12.5 vs 8.4 months)[25]. DESTINY-Gastric02, a single-arm phase II trial of T-DXd after progression on trastuzumab also demonstrated significant success with a 42% ORR and median PFS and OS of 5.6 and 12.1 months, respectively.[26] This resulted in FDA approval and incorporation of T-DXd into the NCCN Clinical Practice Guidelines in Oncology (**Table 1**). T-DXd versus ramucirumab/paclitaxel as second-line treatment is currently being evaluated in the phase III DESTINY-Gastric04 study, and T-DXd is being evaluated in the first-line setting, both as monotherapy and in combination with chemotherapy and an anti-PD-(L)1 agent, in the ongoing phase I/II DESTINY-Gastric03 trial (NCT04704934 and NCT04379596). The ASPEN-06 study is currently recruiting patients with HER2-positive metastatic GEC who have progressed on prior HER2-directed therapy and are suitable for second or third-line therapy. This is a randomised phase II/III study of Evorpacept (ALX148), a CD47 blocker, in combination with trastuzumab, ramucirumab, and paclitaxel (NCT05002127).

A host of new bispecific antibodies are currently being investigated in the phase II and III settings. Zanidatamab, which simultaneously binds domains II and IV of the HER2 protein, has shown greater activity than the combination of pertuzumab and trastuzumab.[27] The ongoing phase II trial in which this therapy is combined with chemotherapy in the first-line setting reported a high disease control rate (DCR) of 92% (95% CI: 79-98%). The median duration of response (DOR) was 20.4 months (95% CI: 6.8-non-estimable [NE]), with 57% (17/30) having an ongoing response at the data cut-off. In all patients, the median PFS was 12.5 months (95% CI: 7.1-NE), and the median OS was not yet reached. The survival rate at 18 months was estimated to be 87.3%.[28,29] These findings support the use of zanidatamab in combination with chemotherapy as a potential new first-line standard-of-care treatment, which is being investigated in a phase III study with chemotherapy and the anti-PD-1 antibody tislelizumab (NCT05152147).[30]

HER2-Targeted Therapy; Novel Future Directions

Due to the recent success of T-DXd, several ADCs have been developed with the aim to improve the effects of T-DXd, often with enhanced antibody engineering. These include the bispecific ADC zanidatamab zovodotin and disitamab vedotin. Disitamab vedotin utilizes the anti-HER2 antibody hertuzumab, which induces more potent ADCC than trastuzumab.[31]

Cinrebafusp alfa, a first-in-class bispecific antibody-Anticalin® fusion protein that targets HER2 and the co-stimulatory immune receptor 4-1BB on T cells, showed deep and durable responses in a previous phase I study, and is currently being investigated in a two-arm phase II trial in patients with metastatic HER2-positive and HER2-low GEC (NCT05190445).[32]

Anti-HER2 vaccines are in development in early phase studies, such as IMU-131 (HER-Vaxx). A significant potential benefit of vaccination is that active immunization may be able to overcome resistance mechanisms.[33] HER-Vaxx is currently being evaluated in combination with chemotherapy and immune checkpoint blockade (NCT05311176).

In vitro studies of genetically modified T cells expressing a HER2-specific chimeric antigen receptor (CAR) demonstrate the ability to recognize and kill HER2-positive cancer cells.[34] These in vitro studies have resulted in the evaluation of HER2- specific CAR-T cells in early phase trials (NCT04650451). Another development is ^{89}Zr-trastuzumab PET, a HER2-labeled radiotracer, which is promising for distinguishing between HER2-positive and HER2-negative tumours and may have future ability to deliver cytotoxic therapy.[35]

Conclusion

After a plethora of negative studies and little progress in the area, many recent successful trials are altering the treatment landscape of metastatic HER2-positive GEC. For the up to 20% of GEC cases that are HER2-positive there is cause for optimism. With a greater understanding of the emergence of HER2 resistance, repeat biopsies to evaluate HER2 status after progression is of fundamental importance to determine and sequence subsequent therapies. Incorporating new agents into the perioperative environment and the numerous new mechanisms of HER2-targeting being evaluated in the metastatic setting, clinicians will have several treatment options for GEC, which was once believed to be “un-targetable”. To add further excitement to the field, HER2-low disease, previously regarded as “HER2-negative,” is being investigated to be treated with HER2-directed ADC. This may add a new subset of patients with GEC potentially responding to HER2-directed treatment.

Correspondence

Elena Elimova, MD
Email: Elena.Elimova@uhn.ca

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About the Authors

Nadia Ghazali, BMed

Dr. Nadia Ghazali is an Australian-trained physician working as a Clinical Fellow at Princess Margaret Cancer Centre. Her medical journey began in Newcastle, Australia, where she completed her medical training. Now based in Toronto, Canada, she focuses on lung cancer with research interest in precision medicine, liquid biopsy, and global oncology.

Affiliations: Princess Margaret Cancer Centre, Toronto, Canada

Natasha B. Leighl, MD, MMSc, FRCPC, FASCO

Dr. Natasha Leighl leads the Thoracic Medical Oncology Group at the Princess Margaret Cancer Centre, and is Professor in the Department of Medicine, and Adjunct Professor in the Institute of Health Policy, Management and Evaluation at the University of Toronto. She holds the OSI Pharmaceuticals Foundation Chair in Cancer New Drug Development through the Princess Margaret Cancer Foundation. She has published over 350 peer-reviewed papers, has held (as principal or co-investigator) over $800 million in peer-reviewed grant funding. She has mentored many trainees that have gone on to leadership roles in oncology around the world, and received the American Society of Clinical Oncology Excellence in Teaching Award in 2019. Dr Leighl's main interest is in developing new treatments in lung cancer and improving lung cancer diagnostics including liquid biopsy. She is involved in clinical studies of novel agents for the treatment of thoracic cancers, has led several international and cooperative group studies in lung cancer and has served as a member of the Lung Disease Site Group Executive of the Canadian Cancer Clinical Trials Group. She was Co-Chair of the CCTG Committee on Economic Analysis, Congress Co-President of the 2018 World Conference in Lung Cancer, and serves on multiple committees including the ASCO Thoracic Guidelines Advisory Group, is co-section editor of The Oncologist and Current Oncology, an editorial board member of the Journal of Thoracic Oncology, British Journal of Cancer, a member of the IASLC Quality and Value Committee, on the Scientific Advisory Board of the Lung Cancer Foundation of America, and was recently elected to the Board of Directors of the Americas Health Foundation. Previously she served as Web Editor of the Journal of Thoracic Oncology, on the editorial board of the Journal of Clinical Oncology, the Royal College of Physicians & Surgeons of Canada Medical Oncology Examination Board, and is Past President of Lung Cancer Canada.

Affiliations: Princess Margaret Cancer Centre, Toronto, Canada

Current Uses and Pitfalls of Liquid Biopsy in NSCLC

Nadia Ghazali, BMed
Natasha B. Leighl, MD, MMSc, FRCPC, FASCO

Introduction

Liquid biopsy has emerged as an important tool in the diagnosis and management of lung and other cancers. Various analytes and analytical methods have been studied, including genomic testing by next-generation sequencing (NGS) and non-NGS approaches, including those examining methylation or DNA fragment size. Liquid biopsy, especially from plasma or blood, has several advantages over percutaneous or endoscopic tissue biopsy. It is less invasive, can be used serially for monitoring, and better reflects tumoural heterogeneity across metastatic sites, as opposed to a single area of the biopsied tumour. Herein, we highlight the current uses of liquid biopsy using circulating tumour DNA (ctDNA) analysis in routine clinical practice and potential pitfalls.

Liquid Biopsy for Initial Tumour Genotyping in Advanced NSCLC

The International Association for the Study of Lung Cancer (IASLC), National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO) recommend using validated and sensitive plasma ctDNA assays in routine clinical practice to ensure timely complete genotyping for patients with advanced non-small cell lung cancer (NSCLC) and other tumour types.[1-4] Complete tumour genotyping, in addition to pathologic subtype and programmed cell death ligand 1 (PD-L1) assessment, is essential for optimal treatment selection in advanced NSCLC and other advanced cancers. Based on genotyping and PD-L1 immunohistochemistry results, therapeutic options range from matched targeted therapy for patients with actionable alterations in their tumours to immunotherapy or chemo-immunotherapy for those without alterations or incomplete genotyping results.

Although tissue NGS is considered the gold standard, performing NGS on liquid biopsy plasma ctDNA samples has been shown to be non-inferior to tissue NGS. Additionally, it can significantly improve the rate of complete genotyping, meaning that a higher percentage of genomic alterations can be identified and characterized using liquid biopsy. Plasma NGS also has a quick turnaround time leading to faster available results.[5-7] Plasma and tissue NGS results are highly concordant, and resulting treatment choices have similar outcomes, whether alterations are detected in plasma or tissue.[6-9] Furthermore, both assessments have minimal risk of false positive results with validated assays. Thus, if an actionable alteration is identified in plasma before tissue results are available, clinicians should use the plasma results to start treatment.[10] As liquid biopsies have lower sensitivity than tissue testing, especially for detecting translocations and copy number variants (e.g. amplification), clinicians should consult tissue NGS results to determine the treatment approach if no actionable alteration is identified in plasma.

IASLC, NCCN, and ESMO guidelines recommend multiple approaches for the integration of liquid biopsy into routine care for patients with advanced NSCLC (**Figure 1**).[1-3] A sequential approach, ordering liquid biopsy after failure of tissue testing to obtain complete genotyping, can prevent repeat biopsy if there is insufficient tissue for genotyping. Complementary or concurrent plasma ctDNA testing improves the rate of complete genotyping and accelerates the time to results.[5-7, 9-12] For example, adding plasma testing to routine tissue testing increased the number of patients detected with targetable alterations in tumour by 15% compared to tissue NGS alone.[7] The concurrent approach of testing both plasma and tissue upfront is recommended by the NCCN and ESMO, particularly for patients with treatment-naïve advanced NSCLC.[2,3] Finally, a "plasma-first approach" has been used when insufficient or no tissue is available for NGS. Liquid biopsy before diagnosis in patients with suspected advanced lung cancer has been shown

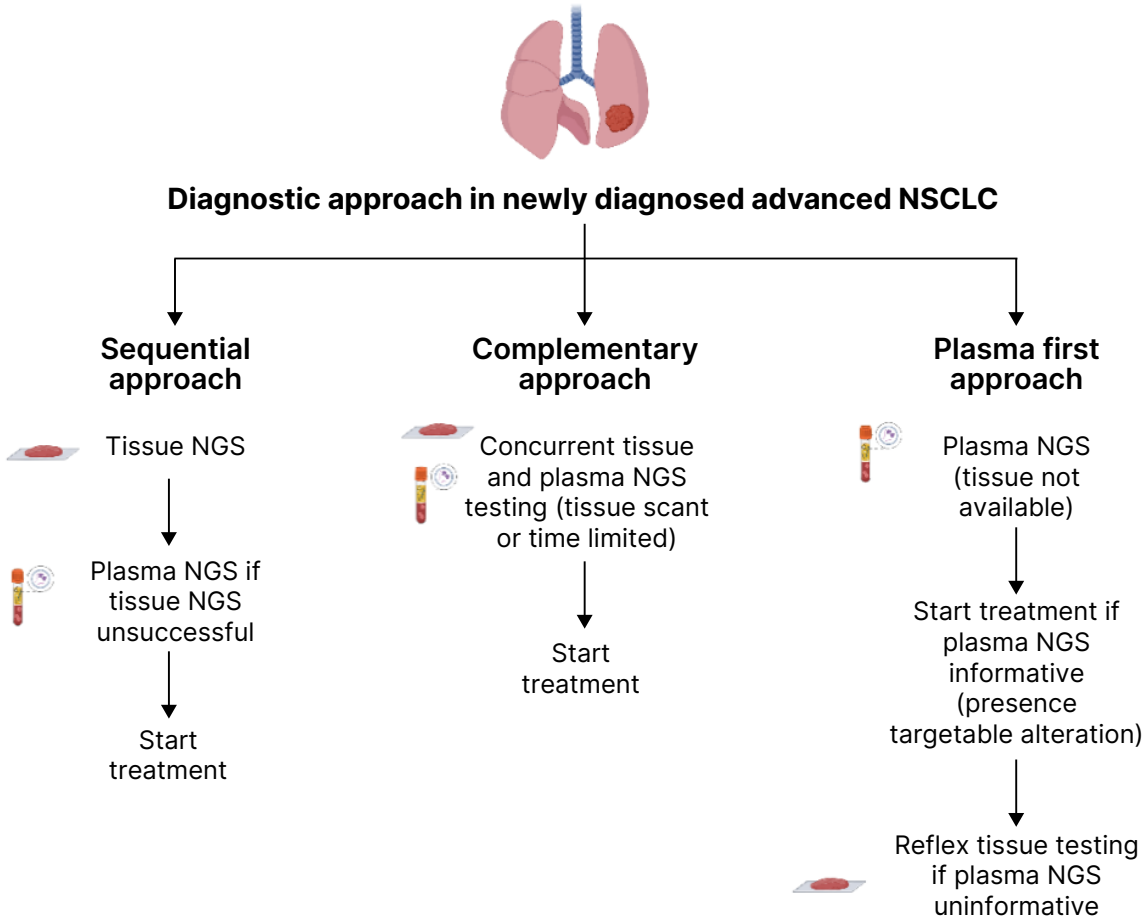

Figure 1. Liquid biopsy approaches for patients with newly diagnosed advanced NSCLC; *created with BioRender.com.*

Abbreviations: NGS: next-generation sequencing; **NSCLC:** non-small cell lung cancer.

to significantly accelerate time to treatment by approximately 35–45% across multiple studies.[9-12]

Liquid Biopsy to Detect Molecular Resistance

Liquid biopsy, specifically plasma ctDNA NGS testing, can be used to detect genomic mechanisms of resistance (MOR) after lung cancer progression on targeted therapy. As tumours evolve, novel genetic alterations and subclonal populations can emerge. Liquid biopsy provides a more comprehensive representation of tumour heterogeneity than single-site tumour tissue biopsies and can prevent repeat tumour biopsy if the plasma result is informative.[13] Initial testing for the epidermal growth factor receptor (EGFR) mutation *EGFR* T790M with liquid biopsy after treatment with first- or second-generation tyrosine kinase inhibitors (TKIs) (e.g. gefitinib, afatinib) is recommended by international guidelines to identify patients that may benefit from third-generation TKIs (e.g. osimertinib).[1-4] Studies have shown that up to 60% of patients may be spared from repeat tumour biopsy using a plasma-first approach.[14]

With the recent shift to the use of third-generation TKIs as initial treatment, molecular resistance to treatment has become more complex.[15] However, both on-target and off-target molecular bypass pathways (e.g. C797S or G724 mutations), *MET* amplification, or emergent fusions may contribute to resistance. Similarly, in *ALK*- and *ROS1*-driven lung cancers, specific resistance mutations, such as *ALK* G1202R or *ROS1* G2302R, may be detected in plasma and direct the use of more specific inhibitors of resistance mutations (e.g. lorlatinib, repotrectinib). Caveats to this

approach include the lower sensitivity of plasma testing than tumour (e.g. *MET* amplification), and the need for tissue to diagnose histologic transformation. However, repeat tumour biopsy and successful tissue NGS after progression on osimertinib are not possible in many patients, supporting a complementary approach.[16]

Liquid Biopsy to Resolve Diagnostic Uncertainty

Interpreting diagnostic imaging in the setting of potential recurrence or progression can be challenging. For example, ground glass changes, parenchymal thickening, and growing atelectatic lesions may be related to cancer progression or treatment complications, such as pneumonitis and post-surgical or post-radiation change. While obtaining pathologic confirmation via biopsy or other invasive methods is the gold standard, liquid biopsy may help resolve diagnostic uncertainty. For example, for patients with tumours with oncogene addiction, a liquid biopsy of ctDNA may detect the return of the original mutation or the appearance of a resistance mutation. The TRACERx study in patients with early-stage lung cancer demonstrated that ctDNA using a tumour-informed assay predicted relapse in 79% of equivocal cases with lymph node enlargement on imaging.[17] Further validation of this approach will help facilitate its routine clinical use.

Emerging Uses - Liquid Biopsy for Treatment Monitoring and Minimal Residual Disease (MRD) Detection

Monitoring Treatment Response in Advanced Disease

Liquid biopsy using plasma is an ideally suited disease monitoring approach during treatment. The presence of plasma ctDNA is a strong prognostic marker across all stages of the disease, with higher levels corresponding with greater tumour burden, greater metastatic potential, and worse prognosis.[18] Clearance or reduction of ctDNA levels is also prognostic, as it is associated with therapy response and better outcomes in advanced and early stages of lung cancer treated with all types of therapy available.[19-21]

The APPLE trial explored the utility of serial monitoring of T790M using plasma ctDNA in patients with advanced EGFR-mutant NSCLC. Molecular progression was identified in 17% of patients in the plasma monitoring arm before radiologic progression, and this early detection of T790M enabled a timely switch from gefitinib to osimertinib.[22] However, median progression-free and overall survival were not significantly different between the arms and the impact of early switching on patient quality of life or symptoms has not been reported.

The optimal cut-off for changes in ctDNA levels to initiate treatment modifications remains under exploration.[23] Studies using adaptive designs to escalate treatment based on ctDNA response after initial therapy are underway. Yu *et al*. are leading a study in which patients that do not clear ctDNA after initial osimertinib are randomized to continue osimertinib alone or add chemotherapy (NCT04410796). Anagnastou *et al*. are studying patients receiving initial pembrolizumab, randomizing those without molecular response to continue immunotherapy alone or add chemotherapy (NCT04093167).

Use of Minimal Residual Disease (MRD) in Early-Stage NSCLC

The detection of ctDNA in plasma, either pre- or post-curative therapy, is a strong prognostic marker in early-stage NSCLC. Chauduri *et al*. demonstrated that MRD detection by ctDNA precedes radiographic detection by a median of 5.2 months in 72% of patients, which was confirmed by other studies.[19]

However, the clinical utility of using MRD to guide treatment decisions remains uncertain. In the adjuvant setting, ctDNA detection using sensitive tumour-informed assays post-surgery is prognostic but cannot identify a population that does not require adjuvant therapy.[24] Clearance of ctDNA after preoperative chemo-immunotherapy has been shown to strongly associate with pathologic complete response (pCR) in several studies, although it may not be specific enough as a single predictive variable.[25,26] Withholding further adjuvant treatment from those that achieve ctDNA clearance has not yet been shown to be safe. Ongoing studies examine the utility of escalating adjuvant therapy in patients with resected Stage NSCLC (NCT04966663) and de-escalating therapy in those with Stage II NSCLC.

Limitations of Liquid Biopsy

Despite the many uses of liquid biopsy in lung cancer, some limitations have yet to be overcome. The lower sensitivity of ctDNA NGS

compared to tumour tissue NGS is the main challenge for the current clinical use of liquid biopsy in lung cancer.[5] In cases with negative ctDNA NGS results, performing additional tissue NGS is recommended. Plasma testing is also less sensitive for the assessment of certain genomic alterations, such as fusions and copy number gain (e.g., *MET* amplification), and the use of RNA-based assays and switching to tissue testing in the case of negative results are recommended.

False-negative results with liquid biopsy are most commonly associated with low tumour DNA shedding to a level below an assay's technical limit of detection.[1] This is important for patients with low tumour burden (especially in those with <1 cm^3 of solid tumour) and those with minimal tumour shedding (e.g. isolated central nervous system [CNS] metastasis).[27] There are additional considerations in the collection and processing of specimens to ensure that DNA or RNA is not significantly degraded before analysis.[1] False positive results can occur in the context of genomic heterogeneity of the tumour. Somatic mutations from the proliferation of clonal blood cell populations may lead to false positive results, known as clonal hematopoiesis of indeterminate potential (CHiP). These variants can be mistakenly identified as cancer-associated mutations, and should be corrected for by using leukocyte sequencing or bioinformatic methods. Fortunately, CHiP alterations do not overlap with current actionable alterations in lung cancer, although they are relevant in treatment response monitoring and MRD detection.

As the use of liquid biopsy moves to early-stage disease, more sensitive assays will be required, although with improved sensitivity may come with a higher risk of false positive results. This may be overcome through use of tumour-informed assays.[28] However, generating tumour-informed assays requires tissue, time, and greater cost, which may limit uptake in routine clinical use. Novel tumour-informed and uninformed ("off the shelf") assays are under development, including uninformed assays for lung cancer screening.[29]

Cost remains an important barrier to reimbursement and widespread implementation in many countries. Single gene assays performed with droplet digital polymerase chain reaction (ddPCR) are less expensive and faster to perform than broader NGS assays. They can be highly sensitive but have limited application.[30] The increased cost of testing with using NGS may be offset by subsequent treatment costs.[7] In addition, the expertise required for these technologies may further restrict routine clinical uptake, with the need to standardize pre-analytical, analytical, and post-analytical methods to ensure consistency.

Summary

Liquid biopsy is an important tool for clinicians treating patients with lung cancer to ensure access to precision medicine and optimal treatment outcomes. Liquid biopsy using plasma ctDNA testing is now recommended by international guidelines for routine use in advanced treatment-naïve NSCLC and as a triage test in tumours resistant to targeted therapies (**Table 1**). Liquid biopsy has been consistently shown to improve the rate of complete genotyping, lead to faster genomic results, and accelerate time to treatment. These factors, in turn, lead to better patient outcomes, less need for repeat biopsies, and fewer missed opportunities for precision medicine. Guidelines do not yet recommend the use of ctDNA for treatment monitoring, including for MRD in early-stage disease, nor for use in adapting treatment. There is active ongoing research to demonstrate and guide clinical utility in these areas.

Despite the advantages of liquid biopsy, there are limitations, including its lower sensitivity, leading to false-negative results and increased testing costs compared to tissue NGS. As the field of liquid biopsy in lung and other cancers continues to evolve, ongoing research will lead to expanded indications for the utilization of liquid biopsy in routine clinical practice.

Indication for ctDNA use	ESMO	NCCN	IASLC	ASCO
Validated, sensitive ctDNA assays can be used to genotype advanced NSCLC and other advanced cancers	✓	✓	✓	✓
Initial genotyping with ctDNA assays should be considered when tissue is unavailable and/or rapid results are needed	✓	✓	✓	✓
Validated ctDNA assays can be used in TKI resistance (NSCLC)	✓	✓	✓	✓
Caveats – ctDNA assays limited by false-negative results, lower sensitivity for fusions, copy number variants → if negative results, reflex to tissue testing	✓	✓	✓	✓
Use of ctDNA/CTC assays to detect minimal residual disease; treatment monitoring not yet recommended	X	X	X	X

Table 1. Current guideline recommendations for liquid biopsy in lung cancer [1-4]; *courtesy of Nadia Ghazali, BMed and Natasha B. Leighl, MD, MMSc, FRCPC, FASCO*

Abbreviations: ASCO: Americal Society of Clinical Oncology; **CTC:** circulating tumour cell; **ctDNA:** circulating tumour DNA; **ESMO:** European Society for Medical Oncology; **IASLC:** International Association for the Study of Lung Cancer; **NCCN:** National Comprehensive Cancer Network; **NSCLC:** non-small cell lung cancer; **TKI:** tyrosine kinase inhibitor.

Correspondence

Natasha Leighl, MD, MMSc, FRCPC, FASCO
Email: Natasha.Leighl@uhn.ca

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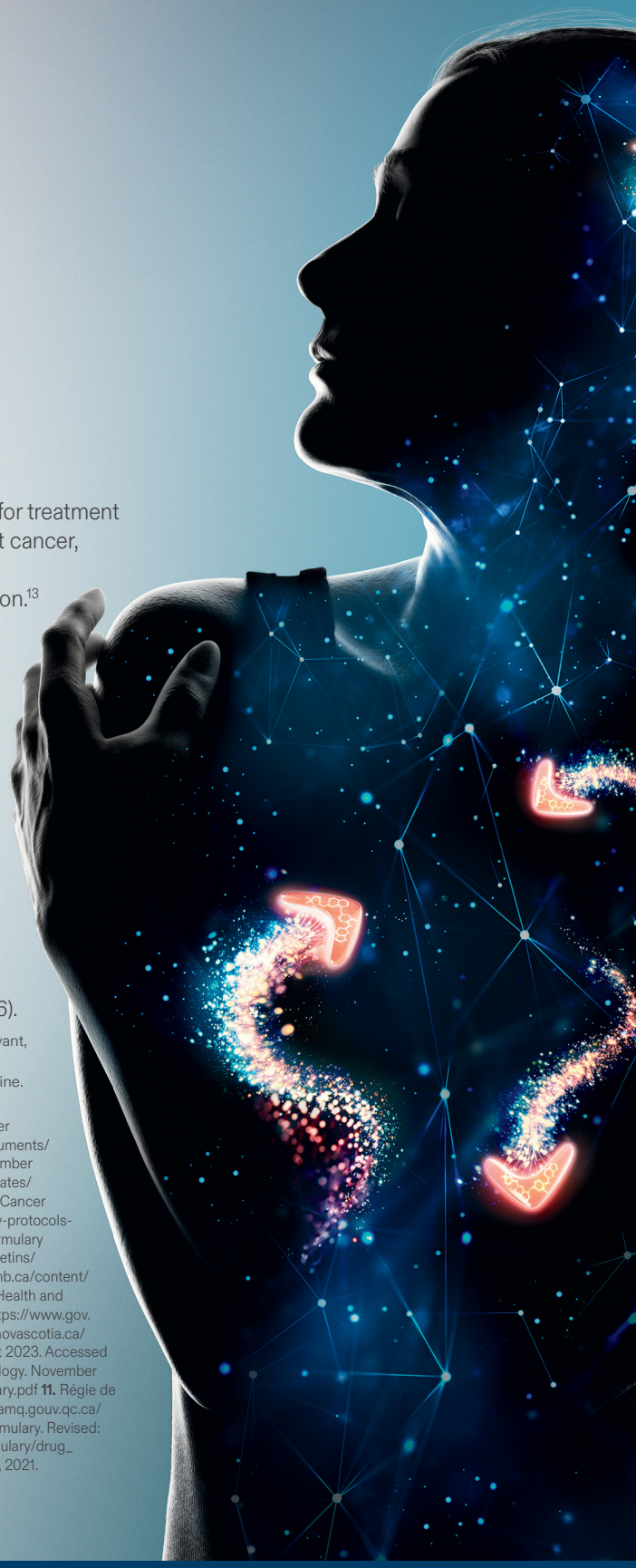

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*The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.[13]

HER = human epidermal growth factor receptor; MBC = metastatic breast cancer; T-DM1 = trastuzumab emtansine.

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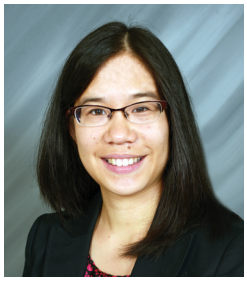
About the Authors



Meredith Li, MD

Dr. Meredith Li is a breast oncology clinical research fellow at the Princess Margaret Cancer Centre, returning after having left for her medical oncology and internal medicine residency upon graduating from medical school at the University of Toronto. She is actively involved as a sub-investigator in various clinical trials. Her research interests range from breast cancer evaluation with imaging and ctDNA to therapeutics. She also enjoys teaching and is working towards the Master Teacher certification from the Department of Medicine at University of Toronto.

Affiliations: Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

David W. Cescon, MD, PhD, FRCPC

Dr. Cescon is a breast medical oncologist and clinician scientist at the Princess Margaret Cancer Centre. His research program integrates laboratory, translational, and clinical studies, focusing on identifying therapeutic vulnerabilities, mechanisms of drug response and resistance in breast cancer, and the integration of liquid biopsy biomarkers. Dr. Cescon chairs the Canadian Cancer Trials Group IND Committee and co-chairs the NCI NCTN Correlative Sciences Committee. He is actively involved in designing and executing numerous breast cancer clinical trials, spanning from early phase to Phase 3.

Affiliations: Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

From Intractable to Treatable: Milestones and Horizons in the Management of HER2+ Breast Cancer

Meredith Li, MD
David W. Cescon, MD, PhD, FRCPC

Introduction

The human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family that initiates various signalling pathways that control cell proliferation and tumourigenesis.[1,2] Historically, approximately 15% of breast cancers have been characterized by overexpression or amplification of HER2, known as "HER2+" breast cancers. This subtype has been associated with an adverse prognosis, along with a high risk of recurrence and worse survival outcomes. However, with the discovery and subsequent development of HER2-targeted therapies, the clinical course of HER2+ breast cancers has fundamentally changed. Optimizing therapeutic strategies using existing and emerging HER2-targeted therapies to build upon these advances remains a major priority for clinical development and treatment delivery.

In 1998, the American Food and Drug Administration (FDA) and Health Canada approved trastuzumab, the first HER2-targeted therapy. Trastuzumab, a monoclonal antibody that binds to the HER2 receptor, has demonstrated clinical activity and improved outcomes in patients with metastatic HER2+ breast cancer when combined with chemotherapy. Following soon after, the first trial of adjuvant trastuzumab (HERA) demonstrated improvements in outcomes when combined with chemotherapy for early HER2+ breast cancer.[3] More than 25 years after its first approval, trastuzumab retains a central role in the treatment of both early and advanced HER2+ breast cancer and has provided a backbone for both new therapeutic combinations (eg. with small molecule inhibitors of HER2) and new classes of therapeutic agents (antibody drug conjugates [ADC]). These successors of trastuzumab are currently redefining the HER2+ treatment landscape in both advanced and early breast cancer.

Metastatic HER2+ Breast Cancer

The current first line treatment of metastatic HER2+ breast cancer, dual antibody therapy with trastuzumab and pertuzumab in combination with a taxane, was established by the CLEOPATRA trial. This study, which was the initial basis for approval of pertuzumab in 2012, demonstrated a significant improvement in both progression-free survival (PFS) and overall survival (OS) with the addition of pertuzumab to trastuzumab and docetaxel, with modest increases in treatment toxicity.[4,5] Shortly thereafter, the ADC trastuzumab-emtansine (T-DM1) displaced lapatinib (a HER2 tyrosine kinase inhibitor [TKI]) and capecitabine in the second line setting, and held this position for nearly a decade (**Figure 1**).

In 2019, a new ADC trastuzumab-deruxtecan (T-DXd) was approved by the FDA after the DESTINY-Breast02 trial showed markedly improved PFS and OS in metastatic HER2+ breast cancer patients who had already received and were resistant to T-DM1 compared to other chemotherapy treatments of physician's choice (PFS 17.8 months for those treated with T-DXd versus 6.9 months for those who received treatments of physician's choice, hazard ratio [HR] 0.36; OS 39.2 months for those treated with T-DXd versus 26.5 months for those who received treatments of physician's choice, HR 0.66).[6] The efficacy of T-DXd, which delivers a topoisomerase I inhibitor payload, was particularly noteworthy, especially given that this class of cytotoxic agent previously had no established

role in the treatment of breast cancer. T-DXd was associated with pneumonitis occurring at a rate of approximately 10% with two reported grade 5 deaths; thus, although T-DXd is certainly a potent treatment agent, its use requires careful monitoring.

T-DXd was then compared to the second line standard T-DM1 in patients who had progressed on a trastuzumab- and taxane-containing regimen in the DESTINY-Breast03 trial, which subsequently led to the approval of T-DXd as a second line treatment. Updated results showed a PFS of 28.8 months with T-DXd and 6.8 months with T-DM1 (HR 0.33), which is the longest reported PFS in the second-line setting.[7]

The DESTINY-Breast03 trial excluded patients with active brain metastases but did include 15% of patients with clinically inactive brain metastases or stable brain metastases that were previously treated and were no longer symptomatic. Within this subgroup, a substantial PFS advantage favouring T-DXd was observed (15 months for those treated with T-DXd versus 5.7 months for those receiving other treatments, HR 0.38), suggesting that T-DXd has intracranial activity in patients with stable brain metastases.[7] These findings, complemented by data from smaller trials, have underscored the significant central nervous system (CNS) activity of this agent. Such an outcome might have been unexpected for a large molecule therapy, given the challenges posed by the blood-brain barrier. This is particularly noteworthy in the context of CNS metastases, which have historically been a challenge for HER2 antibody therapies. Furthermore, preliminary evidence suggests that T-DXd has CNS efficacy in patients with active brain metastases, however, data generation is ongoing.

During the intervening decade, a number of other HER2-directed therapies were evaluated, including both small molecule TKIs (eg. neratinib, tucatinib, lapatinib) and monoclonal antibodies (eg. margetuximab). Among these, tucatinib, when used in combination therapy, has become part of the standard treatment regimen, for its overall efficacy and for its notable effectiveness in patients with brain metastases, as demonstrated in the HER2CLIMB trial. The patients enrolled in this study were heavily pre-treated (a median of four prior lines of therapy) and were randomized to receive tucatinib or placebo in combination with trastuzumab and capecitabine. At one year, the PFS was 33% among patients receiving the tucatinib combination compared to 12% among patients not receiving tucatinib. Specifically, among patients with brain metastases, the 1-year PFS rate was 25% in the group treated with tucatinib compared to 0% without tucatinib.[8]

These data can be viewed in the context of previous examinations of HER2 TKIs including neratinib and lapatinib, which demonstrated some intracranial activity in combination with capecitabine in small single-arm phase II trials. Response rates were variable, although some patients did achieve a prolonged clinical benefit. Most of these patients were previously treated with trastuzumab (not T-DM1) and other chemotherapy agents. Although prospective trials of T-DM1 excluded patients with active brain metastases, at least some intracranial activity has also been reported in subsequent case series and trials. Therefore, the intracranial activity of neratinib and lapatinib when used after T-DM1 and tucatinib is not known. Moreover, the intracranial activity of tucatinib, neratinib, and lapatinib have never been directly compared.

The most recently reported phase III trial for advanced HER2+ breast cancer is the HER2CLIMB-02 trial, which evaluated T-DM1 against T-DM1 in combination with tucatinib as a second-line treatment. Primary results presented at the 2023 San Antonio Breast Cancer Symposium (SABCS) showed an improvement in PFS that met the primary endpoint. However, the initial data for OS, while immature, demonstrate a numerical advantage for the placebo arm.[9] Considering these findings and the established role of T-DXd in the second-line setting, the major application of tucatinib is likely to remain in combination with trastuzumab and capecitabine following T-DXd. However, in selected situations, such as for patients with active brain metastases, limited extracranial disease burden, or contraindications to T-DXd, this combination may serve as an alternative to the general approach.

Advancements in systemic treatments for CNS involvement are reshaping clinical management strategies for brain metastases, which have traditionally relied on surgery and radiation therapy (either stereotactic or whole-brain). The optimal integration of these approaches, however, necessitates the generation of prospective evidence to inform evidence-based guidelines. Meanwhile, the prognosis of patients with leptomeningeal disease (LMD) has not changed significantly over the last decade, which calls for increased attention. Limited data

Figure 1. Approval of anti-HER2 therapies; *courtesy of Meredith Li, MD and David W. Cescon, MD*

exist for both T-DXd and tucatinib combinations in LMD. The CLIMB-LMD trial (NCT06016387) is a Canadian investigator-initiated study evaluating the efficacy of radiation therapy followed by tucatinib, trastuzumab, and capecitabine in patients with HER2+ LMD in any line of treatment.

Looking Forward

Despite these developments, there is still a significant amount of work required to refine clinical management with existing agents and to develop the numerous new agents currently under investigation. Several trials are currently underway to challenge the first-line standard treatment of trastuzumab, pertuzumab and taxane. The DESTINY-Breast09 trial (NCT04784715) is evaluating T-DXd with or without pertuzumab in this context. Given the proven efficacy of T-DXd in later lines of treatment, this trial is important. However, the potential tolerability benefits of maintenance therapy with trastuzumab and pertuzumab need to be balanced against the more toxic profile of T-DXd. Additionally, while the primary endpoint is PFS, understanding the impact on OS, and ensuring adequate delivery of second-line T-DXd in the study population, will be crucial to assess the true impact of this strategy. Alternative maintenance regimens following induction with taxane, trastuzumab, and pertuzumab are also being evaluated, such as the addition of tucatinib in the HER2CLIMB-05 trial (NCT05132582), the phosphatidylinositol 3-kinase (PI3K) inhibitor inavolisib for PI3K-p100α (PIK3CA) mutated disease in the INAVO122 trial (NCT04191499), or novel endocrine agents.

At the other end of the spectrum, there are a large number of investigational anti-HER2 therapies being evaluated principally for drug resistant disease. Understanding the mechanisms of resistance to established agents and how to prioritize the development of new agents based on identifiable biomarkers is likely to be important for this increasingly complex therapeutic arena.

Early HER2+ Breast Cancer

The evolution of systemic therapy for early HER2+ breast cancer has followed a general approach of de-escalating therapy for low-risk patients and escalating therapy for higher-risk patients. Identification of low-risk disease has principally been based on anatomic stage (small tumour size and node negativity), while escalation strategies have taken advantage of response assessment to neoadjuvant therapy and the prognostic value of residual disease after pre-operative antibody-based chemotherapy combinations.

In the single arm phase II APT trial, patients with resected small (<3 cm) node-negative HER2+ cancers were treated with single-agent paclitaxel rather than multiagent chemotherapy and trastuzumab to complete one year of treatment. After a median follow-up of 10 years, the safety profile remained excellent, and breast cancer specific survival was a remarkable 98.8%, confirming this de-escalated regimen as the standard of care for patients with low-risk/node negative disease.[10]

The phase II NeoSphere trial included patients with higher risk (>2cm or node positive) HER2+ early breast cancer. The findings indicated that dual HER2 blockade with trastuzumab and pertuzumab in combination with chemotherapy significantly improved the rate of pathologic complete response (pCR) compared to trastuzumab and chemotherapy (45.8% vs 29% in the trastuzumab group).[11] Consistent with the recognized prognostic association of pCR in HER2+ breast cancer, patients from any treatment group who achieved a pCR had a longer PFS than those who did not achieve a pCR. Notably, PFS was numerically improved at five years (HR 0.69). However, this difference was not statistically significant because the study was not powered to definitively assess this secondary endpoint.[12]

The improvements in pCR rates achieved with neoadjuvant dual HER2 blockade allows for

the avoidance of an adjuvant course of T-DM1, which is currently the standard treatment for patients with residual disease. This approach was established by the KATHERINE trial, which demonstrated improved outcomes compared to completing adjuvant trastuzumab for patients who had residual invasive cancer following neoadjuvant therapy. The trial found that T-DM1 reduced the risk of invasive disease recurrence at 3 years by 50% compared to trastuzumab (invasive disease-free survival [iDFS] was 88.3% in the T-DM1 group and 77% in the trastuzumab group). Furthermore, distant recurrence as the first invasive disease event occurred in 10.5% of patients in the T-DM1 group compared to 15.9% in the trastuzumab group.[13] Based on these results from the KATHERINE trial, T-DM1 was approved for adjuvant use by the FDA and Health Canada in 2019, establishing this adjuvant regimen and solidifying the neoadjuvant approach necessary for its delivery.

Within the framework of neoadjuvant response-guided use of adjuvant T-DM1, several unanswered questions remain, particularly concerning the role of pertuzumab in patients who achieve a pCR. The APHINITY trial compared 1 year of adjuvant pertuzumab and trastuzumab with trastuzumab alone in patients with node-positive or high-risk node-negative HER2+ breast cancer. The trial demonstrated an improved iDFS at six years (91% versus 88%, respectively).[14] The benefit was mostly driven by the node-positive cohort; the node-negative cohort derived no benefit. The interim survival analysis also did not reach statistical significance for benefit. Whether the impact of an adjuvant course of pertuzumab can be extrapolated to the subset of patients who achieve a pCR with neoadjuvant therapy who continue with trastuzumab is unknown.

Ongoing Development of Adjuvant Therapy for Residual Disease

Given the improvements observed with newer HER2 therapies for metastatic disease, there has been substantial interest in evaluating these agents in early breast cancer. In particular, T-DXd and tucatinib have been a focus of such efforts, with ongoing phase III trials underway. In addition to improving overall outcomes with the delivery of more effective therapy, the CNS activity of these agents offers the hope that CNS recurrences, which comprise 7% of distant recurrences,[15] can be reduced.

While residual disease has been useful to identify patients for treatment with adjuvant T-DM1, this strategy nevertheless results in overtreatment of a considerable proportion of patients, especially considering that the distant recurrence-free survival at 7 years for participants treated with adjuvant trastuzumab was 78.5%. An update of the KATHERINE trial presented at the SABCS 2023 showed that the subgroup of patients with small residual disease up to ypT1b and ypN0 (<1 cm and negative axillary lymph nodes) did have a meaningfully improved iDFS at 7 years with T-DM1 (85.7%, T-DM1 versus 76.7%, trastuzumab), though no difference in OS has been observed in this exploratory subset.[15] Escalating beyond T-DM1 creates further potential overtreatment. Therefore, improving outcomes necessitates identification of the subpopulations at higher risk. The extent of residual disease, as discussed earlier, remains strongly prognostic and other clinical features such as ER (estrogen receptor) status (iDFS 83.1% for ER+ versus 75.0% for ER- disease), and HER2 score (iDFS 82.8% for IHC 3+ versus 72.4% for IHC 2+) are associated with outcomes following adjuvant T-DM1.[15] Diagnostic tools employing tumour-based gene expression analysis, similar to those employed

for ER+/HER2-negative disease, are currently under development.[16] and may offer an additional opportunity to refine risk estimates.

Recent advances in technologies for the detection of circulating tumour DNA (ctDNA) in "liquid biopsies" present an additional opportunity to individualize treatment escalation for adjuvant therapy.[17] Highly sensitive and specific ctDNA tests, designed expressly for this purpose, can detect ctDNA "molecular residual disease" (MRD) in patients prior to clinical recurrence. Retrospective analyses have demonstrated that such detection may risk stratify individuals with residual disease, and that the detection of ctDNA (in the absence of a subsequent change in therapy) is associated with an extreme risk of recurrence. Such assays thus enable the development of strategies to identify and "intercept" recurrences with treatment escalation and can also provide a measurable surrogate of disease that may reflect treatment response.

We are actively exploring this question through the KAN-HER2 MRD (NCT0538814) trial, a phase II study enrolling patients with pathological residual disease following neoadjuvant therapy who are recommended standard adjuvant T-DM1 therapy. In the initial 4 to 6 cycles of T-DM1 therapy, participants are monitored using ctDNA surveillance via a tumour-informed assay. If MRD is detected, their treatment regimen is intensified by adding neratinib (for up to one year) alongside T-DM1 therapy. The primary efficacy outcome for this proof-of-concept study is the clearance of ctDNA, with secondary outcomes of invasive breast cancer-free and distant metastasis-free survival. The findings from this trial are expected to yield significant insights into the effectiveness of this therapeutic combination as well as the feasibility and performance of ctDNA monitoring in this patient population.

Summary

Once a breast cancer subtype linked with a poor prognosis, HER2-positive breast cancer has become highly treatable over the past two decades owing to the advent of HER2-targeted therapies. It is crucial to note, however, that HER2+ breast cancer is a heterogeneous disease in today's clinical context. Therefore, future treatment strategies must be tailored to each individual's disease biology and the clinical behaviour of their disease. Achieving optimal clinical outcomes while minimizing treatment-related toxicities calls for the development and application of precise diagnostic tools to accurately assess each individual's risk, and the selection among available therapies requires a refined understanding of predictive biomarkers for these treatments. Finally, ongoing development of new therapeutic agents necessitates a deeper insight into tumour evolution and resistance mechanisms, advancing the groundwork laid by the introduction of trastuzumab.

Correspondence

David W. Cescon, MD, PhD, FRCPC
Email: Dave.Cescon@uhn.ca

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About the Authors

Marco Pisino, MD

Dr. Pisino is a medical oncologist at the “Vito Fazzi” Hospital in Lecce, Italy, with a clinical practice specializing in genitourinary malignancies. He completed his medical degree and training at the University of Parma, followed by an oncology residency at the University of Bari. Most recently, he pursued a fellowship in Genitourinary Oncology through the Italian Foundation “La Clessidra” at the University of British Columbia under Dr. Lucia Nappi’s supervision, with a research focus on testicular cancer.

Affiliations: Division of Medical Oncology, Vito Fazzi Hospital, Lecce, Italy

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Lucia Nappi, MD

Dr. Lucia Nappi is a medical oncologist - clinician scientist, MD and PhD. She is an assistant professor in the department of Urologic Sciences at the University of British Columbia and a senior research scientist at the Vancouver Prostate and works as medical oncologist in the GU group at the BC Cancer in Vancouver. Her main research focus involves the discovery and validation of biomarkers in GU cancers, mainly in prostate and testis cancer patients. She has got several grants and awards including the Prostate Cancer Foundation Young Investigator award and the Michael Smith Foundation Health Professional Investigator award (2020), the operational CIHR grant in 2021, the R37 NIH grant and the career development award from the US department of defense (2022). She is the vice-chair of the SWOG Adolescent and Young Adults (AYA) committee and the chair of the international SWOG-S1823/CCTG GCC.1 clinical trial.

Affiliations: Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada
British Columbia Cancer – Vancouver Centre, Department of Medicine – Division of Medical Oncology, University of British Columbia, Vancouver, BC, Canada

Survivorship Issues in Testicular Cancer

Marco Pisino, MD
Lucia Nappi, MD

Introduction

Testicular cancer (TC) is the most prevalent tumor in young men aged 15–40 years,[1] with an annual incidence of 3–11 new cases per 100,000 males in Western countries.[2] In 2020, the International Agency for Research on Cancer reported 74,458 newly diagnosed cases of TC globally.[3] The etiology of TC is complex and includes both genetic and environmental factors. The prognosis of TC is excellent with a >90% cure rate and a >95% 5-year survival rate with appropriate treatment.[4] Treatments for TC include active surveillance, chemotherapy, radiotherapy, and retroperitoneal lymph node dissection, depending on the clinical stage and tumor subtype. It is crucial that patients receive information on the diagnosis, therapeutic management options, consequences of treatments, and surveillance protocols, which allows the patient to play an active role in the decision-making process. Fear of recurrence often affects TC survivors. Therefore, it is essential to fully involve the patient in the choice of the treatment to ensure an optimal compliance, especially when selecting the active surveillance strategy.[5] In the modern era, in light of the excellent outcomes achieved in TC management, one of the high priorities is to deliver curative treatments while minimizing long-term toxicity. This focus can have a positive impact on quality of life and life expectancy of TC survivors.

Chemotherapy Toxicities

The most common chemotherapy regimens for TC treatment are cisplatin-based and include bleomycin, etoposide, and cisplatin (BEP) or etoposide, ifosfamide, and cisplatin (VIP). In cases in which the disease persists after initial chemotherapy, several successful salvage strategies are available, including either standard or high-dose chemotherapy approaches.[6]

Lung toxicity. The most severe and life threatening adverse effect of bleomycin is lung toxicity, characterized by dry cough, dyspnea, tachypnea, cyanosis, decreased exercise tolerance, and fever.[7] Short-term respiratory complications at 3 years occur in up to 46% of patients (usually mild, self-limiting), however, a small fraction of patients may develop pulmonary fibrosis which carries a 10% mortality rate.[8] Owing to fibrotic transformation in both lungs, with reticular opacities and the typical honeycomb pattern, interstitial lung diseases are more easily diagnosed using high-resolution computed tomography scans.[9] Pre-treatment pulmonary function tests may be useful to monitor toxicity on treatment. An international study involving 38,907 patients demonstrated that the relationship between bleomycin and the development of pulmonary fibrosis had a statistically significant association with an increased risk of mortality from respiratory disorders.[10] In addition, the cumulative dose, age at diagnosis, smoking history, renal impairment, and mediastinal radiation treatment are also risk factors for bleomycin-associated pneumonia.[11]

Nephrotoxicity. It is well known that cisplatin damages the proximal and distal renal tubule epithelium and renal collecting duct system, as well as the glomeruli at higher doses.[12] Two long-term studies reported a persistent reduction in renal function in testicular cancer survivors (TCS) for many years after completion of chemotherapy compared to their baseline renal function.[13,14] Furthermore, a Norwegian study involving 85 patients showed that more than 10 years after the end of treatment renal function was reduced by 14% among TCS who received chemotherapy, and by 8% in patients receiving radiotherapy alone.[14] To limit the severity of kidney damage, healthcare professionals should administer hydration and avoid nephrotoxic drugs during cisplatin-based chemotherapy.

Peripheral neuropathy. After cisplatin-based chemotherapy, 20–40% of patients develop chronic peripheral neuropathy symptoms owing to the neurotoxic effect of cisplatin.[15,16] Chronic peripheral neuropathy tends to improve gradually within a few months after the conclusion of treatment. However, in some patients the damage becomes chronic and does not regress.

It is important to point out that the risk of cisplatin-induced peripheral neuropathy is related to its cumulative dose.[17] In the majority of patients, peripheral neuropathy resolves within 12 months, although it could persist beyond this timeframe in approximately 17% of the patients.[18]

Ototoxicity. Cisplatin is known to selectively damage the outer hair cells of the cochlea, causing tinnitus and high frequency hearing loss.[19] Severe ototoxicity has been independently associated with older age, higher cumulative cisplatin dose, history of noise exposure, hypertension, and baseline renal impairment.[20,21] There are no approved pharmacological treatments or preventative measures for cisplatin-induced ototoxicity. If possible, patients should use ear protection when exposed to loud noises. The 5-day BEP regimen is preferred to a 3-day regimen because maximal cisplatin concentrations may be directly related to the severity of ototoxicity.[22]

Ocular toxicity. Retinal damage has also been associated with cisplatin treatment.[23,24] High dose cisplatin can lead to retinal toxicity and macula pigmentary alterations.[25]

Vascular toxicity. Patients with TC are at a higher risk of experiencing Raynaud's phenomenon. The symptoms usually start within a year after the therapy and primarily affect the fingers. Digital ischemia has been documented in 37% of TC patients receiving vinblastine-and bleomycin-containing combination treatment.[26] Those who smoke daily had a significantly stronger association with Raynaud-like symptoms and paresthesias (with odds ratios ranging from 1.5–2.2) compared to those who never smoked.[27]

Chronic Cancer-Related Fatigue

Fatigue is a common and significant issue for TCS. The causes of fatigue in TCS are multifactorial and consist of physical, emotional, and psychosocial factors, including the cancer itself and the treatments used. Physical fatigue leads to decreased energy levels, muscle weakness, and difficulty in performing routine tasks. Cognitive fatigue, characterized by mental exhaustion and difficulty concentrating, can affect work performance, memory, and decision-making abilities. Chemotherapy and radiation therapy cause long-lasting fatigue owing to their impact on healthy cells and overall energy levels. A Norwegian multicenter study analyzed questionnaires from 1,431 patients concerning the evaluation of cancer-related fatigue and chronic general fatigue and reported a high prevalence of cancer-related fatigue among TCS compared to that of the general population.[28] Another study has shown that in TCS there is a notable increase in chronic fatigue, anxiety, and depression more than 10 years after treatment completion, along with lower testosterone levels. Moderate-to-high physical activity appeared to offer a protective effect.[29]

Avascular Necrosis of the Hip

Avascular necrosis (AVN) of the hip, also known as osteonecrosis of the femoral head, is a debilitating condition that affects 1–2% of long-term survivors of TC. Common signs and symptoms of AVN include persistent pain in the hip joint, limited range of motion, and radiation of pain from the hip joint to the groin or thigh area. Owing to its rarity, most of the reported cases of AVN of the hip are in the form of case reports.[30,31] In AVN, the blood supply to the femoral head is disrupted, leading to the death of bone tissue. Cisplatin-based chemotherapy, especially when it includes high dose corticosteroids used as antiemetics, have negative effects on the blood vessels supplying the hip joint. Radiotherapy directed at the pelvic region can also cause damage to the blood vessels, resulting in an increased risk of AVN.[32] The signs of AVN may be detected using MRI or CT scans. In severe cases of AVN, total hip replacement surgery may be necessary to alleviate pain and restore mobility.[33]

Changes in Serum Testosterone, Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH), Hypogonadism, Fertility, Sexual Dysfunction

Treatments employed in TC can have long-term effects on the endocrine system. Several studies have reported that TCS often experience reductions in serum testosterone levels[34-37] resulting from the direct destruction of Leydig cells, which are responsible for testosterone production. Disruption in the hypothalamic-pituitary-gonadal (HPG) axis can occur with consequent changes in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.[38,39] Low testosterone levels result in various symptoms, including fatigue, decreased

libido, erectile dysfunction, and reduced muscle mass.[40] It is important to monitor hormone levels in TCS and consider appropriate interventions, such as testosterone replacement therapy.
The long-term effects of cisplatin-based chemotherapy on reproductive health and sexual function have become increasingly important. Studies have shown that up to 80% of TCS treated with more than 4 cycles of cisplatin-based chemotherapy experience hypogonadism.[41] The most common causes of hypogonadism are age, testicular dysgenesis syndrome, chemotherapy, or post-orchiectomy radiation. According to a Norwegian study, TCS treated with radiation therapy or chemotherapy had a significantly increased risk of low testosterone levels. Additionally, they showed elevated levels of LH and FSH during long-term follow up. Possible effects of hypogonadism include decreased libido, erectile dysfunction, muscular weakness, osteoporosis, fatigue, and depression.[42] Moreover, TC and its treatments can have a significant impact on fertility. It has been observed that the production of spermatozoa is often reduced or even absent at diagnosis in patients with TC.[43,44] Radiotherapy and chemotherapy treatments have the ability to induce alterations in the quality and quantity of spermatozoa in up to 30% of patients.[45,46] In particular, the greatest impact on the deficiency in the quality and quantity of spermatozoa seems to occur 3–6 months after the end of treatments, with variations related to the specific therapy, dose, and duration of administration. It is also known that the recovery time of spermatogenesis is slower (up to 24 months after the end of treatments) in cases in which more than 3 cycles of chemotherapy were delivered or after radiotherapy.[47] Therefore, it is crucial to discuss fertility preservation options with TC patients before starting treatment.
Erectile dysfunction is caused by the physical and psychological effects of the disease itself, as well as the treatments involved, especially considering that radiotherapy mainly leads to erectile dysfunction, while retroperitoneal lymph node dissection is mainly responsible for ejaculatory dysfunction.[48] Overall, sexual dysfunction has been reported in 30–50% of patients.[49,50]

Finally, vitamin D deficiency has been reported in TC patients. It is unclear if the deficiency is related to the reduced gonadal activation of vitamin D or if it is a pre-existing condition. Some data also suggest a specific association of vitamin D deficiency with specific subtypes of germ cell tumors.[51]

Cardiotoxicity and Metabolic Syndrome

Chemotherapy has been associated with an increased risk of the development of heart failure, arrhythmias, and impaired cardiac function in TCS. A recent retrospective analysis performed on 44,975 U.S. men with TC that is registered in the Surveillance, Epidemiology, and End Results (SEER) database has shown that the most common noncancer cause of death, at least one year after diagnosis, was heart disease.[52] In addition, radiotherapy has been associated with a higher long-term risk of diabetes.[53] Compared to patients only receiving surgery, those treated with radiation therapy or chemotherapy were more likely to receive cardiologic drugs.[54] Several mechanisms have been proposed to explain the cardiotoxic effects of these agents. According to the direct vascular damage hypothesis, cisplatin or bleomycin cause direct damage to blood vessels as demonstrated by an increased release of Von Willebrand factor from endothelial cells.[55] Hypogonadism and testosterone deficiency can also lead to a pro-inflammatory state, endothelial dysfunction, and an increased risk of cardiovascular disease.[56,57] A study involving TCS that included a 4-year follow-up has demonstrated that patients who underwent chemotherapy were more likely to have metabolic syndrome than patients who underwent surgery alone. Furthermore, the incidence of metabolic syndrome was cisplatin dose dependent.[57] Monitoring cardiac function through echocardiography and with electrocardiograms can help detect early signs of cardiotoxicity in TCS.

Risk of Secondary Malignancies and Metachronous Contralateral TC

Over the years, numerous studies have documented an increased risk of second malignancies in TCS. The risk appears to be increased especially after radiotherapy, although chemotherapy alone and the association of radiotherapy and chemotherapy can effectively contribute to the development of secondary tumors. For instance, radiotherapy has been associated with a 1.5- to 4.4-fold increase in the risk of gastrointestinal, lung, and genitourinary cancers.[58] Moreover, the risk of leukemia has been shown to be three times higher in patients

treated with radiotherapy.[59] The risk of cancer after ionizing radiation follows a linear dose-response model.[60] Chemotherapy with cisplatin and etoposide has also been associated with significantly elevated risks of secondary leukemia and a 2-fold greater risk of developing solid tumors compared with surgery alone.[61] Moreover, there is evidence suggesting a significant correlation between the cumulative dose of cisplatin and etoposide, and the risk of leukemia.[62-66] These risks appear to be similar for seminoma and nonseminoma types of TC.[67] Patients treated with both radiotherapy and chemotherapy have the highest risk of developing secondary malignancies.[61,68]

Metachronous contralateral testicular cancer occurs in approximately 1% to 5% of TCS.[69] Younger age and seminoma histology are associated with a higher risk of contralateral involvement.[70,71] Individuals with a family history of TC, cryptorchidism, infertility, or certain genetic abnormalities also have an increased risk of developing contralateral cancer.[55,72-74]

Psychosocial Distress

TC has a profound psychological and emotional impact on TCS. The experience of the diagnosis of TC occurs in a critical period of life in which young people are preparing to become independent, establish intimate emotional relationships, along with the prospect of creating a family, explore their sexuality, and cultivate professional prospects. The desire for normality is strongly felt in these patients. It is not uncommon for survivors to experience anxiety, depression, and feelings of uncertainty about their future. The diagnosis and treatment process can be emotionally challenging, often leading to a sense of loss, body image issues, and sexual concerns. Additionally, survivors may struggle with fear of recurrence, financial burdens, and difficulties in maintaining relationships.[75-78] Furthermore, the physical changes resulting from surgery, chemotherapy, or radiation therapy have a significant impact on body image and self-esteem. The loss of a testicle can lead to an alteration in the perception of oneself and to sexual disorders that affect one's sense of masculinity, which can cause feelings of inadequacy or insecurity. Additionally, the fear of cancer recurrence and the uncertainty surrounding long-term prognosis can create significant psychological distress.[79] This psychological distress impacts their ability to engage in daily activities, maintain relationships, and pursue future goals.[80-82]

However, with proper support and psychological interventions, survivors can effectively manage and cope with psychosocial distress, improving their quality of life.

Taking care of patients with TC necessarily involves the existence of an integrated multidisciplinary team, with specific expertise in communication and the doctor-patient relationship.[5,83-85]

Long-Term Mortality

Although effective treatments and early detection have significantly improved the prognosis for TC patients, the long-term toxicities negatively impact their long-term survival.[10,86-88] High mortality seen with long term follow up has been reported in a Norwegian study that analyzed TC survival in a population-based database. The long-term relative survival (RS) among TC patients was significantly shorter than that of non testis cancer patients, especially after 30 years of follow-up. The authors observed a continuous decline in long-term RS, except for seminomas diagnosed after 1999, owing to the extensive use of adjuvant radiotherapy before that period. RS was also significantly reduced among patients >40 years of age at the time of the diagnosis. The main cause of the decline in RS was attributed to the late toxicity of chemotherapy and radiation therapy.[89]

In conclusion, understanding the long-term mortality of TCS has important implications for their long-term health and well-being. It is important for survivors to be cognizant of these potential risks and take proactive action to mitigate long-term mortality. Changes in treatment modalities, regular follow-up appointments, lifestyle modifications, and participation in supportive care programs are essential components of a comprehensive approach to long-term survivorship.

Correspondence

Lucia Nappi, MD
Email: lucia.nappi@bccancer.bc.ca

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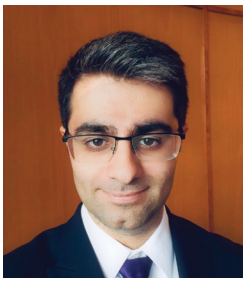
About the Authors



Arman Zereshkian, MD

Dr. Zereshkian is a fourth year Medical Oncology resident at the University of Toronto. He completed his pharmacy degree and undergraduate medical education at the University of Toronto, and completed Internal Medicine training at McMaster University.

Affiliations: Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
University of Toronto, Toronto, Canada

Erica S. Tsang, MD

Dr. Tsang is a GI medical oncologist at the Princess Margaret Cancer Centre and Assistant Professor at the University of Toronto. She completed her Internal Medicine and Medical Oncology training at the University of British Columbia, followed by further training in GI and early phase oncology at the University of California, San Francisco. Her research interests include genomics and clinical trials, with a focus on pancreatic cancer.

Affiliations: Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
University of Toronto, Toronto, Canada

An Evolving Paradigm in Borderline Resectable and Locally Advanced Pancreatic Cancer: Current Strategies and Opportunities for the Future

Arman Zereshkian, MD
Erica S. Tsang, MD

Introduction

Pancreatic ductal adenocarcinoma (PDAC), a cancer of the gastrointestinal tract, has been increasing in incidence, with an estimated doubling worldwide over the past two decades.[1] Despite increases in awareness and innovations in genomics and drug discovery, 5-year survival remains low, at only 10%. This is in part owing to the majority of patients being diagnosed at the advanced stage of the disease, in addition to chemotherapy recalcitrant disease.[2]

Surgical resection is necessary for a potential cure, however, this is only possible for the 10% of patients who present with resectable disease and potentially for those with borderline resectable disease.[3] Locally advanced pancreatic cancer accounts for approximately 30% of those with PDAC and most of those patients are often precluded from curative intent surgery due to major vascular invasion and local infiltration into peri-pancreatic soft tissue. In cases of locally advanced disease, induction chemotherapy is often used, identifying the subgroup of patients more suited for local treatments and those who may later develop metastases. The treatment regimens used for patients with locally advanced PDAC are often extrapolated from trials involving patients with metastatic disease. In some cases, responses to neoadjuvant therapy have allowed for surgical resection, albeit these aggressive resections were associated with significant morbidity.[4]

There is growing interest in identifying the optimal neoadjuvant treatment for patients with borderline resectable pancreatic cancer (BRPC) and locally advanced PDAC (LAPC) in an effort to improve outcomes. Here we review therapeutic strategies for borderline resectable and locally advanced PDAC, with a focus on novel systemic therapy regimens, chemoradiation, and different radiation modalities.

All in the Definition

The definition of “resectability” has been subject to intense debate and remains variable. The National Comprehensive Cancer Network (NCCN) definitions for resectable, borderline resectable, and locally advanced disease are based on arterial and venous involvement; namely, the superior mesenteric artery, celiac axis artery (CAA), common hepatic artery (CHA), superior mesenteric vein, and portal vein (PV) (**Figure 1**).

Evolving surgical techniques have improved resectability in what was previously classified as BRPC. There is also considerable ambiguity on what constitutes borderline resectability, because patients that have LAPC are defined as having BRPC or vice versa.[5,6] In general, patients with BRPC must have <180% abutment of the superior mesenteric artery (SMA), short-segment or small contact with CHA or CAA, whereas patients with LAPC have more than a 180-degree involvement of the SMA. Other guidelines include the MD Anderson Classification (MDACC) and International Association of Pancreatology (IAP), with a slight variance in the CAA, CHA, superior mesenteric vein (SMV), and PV involvement; however, if no

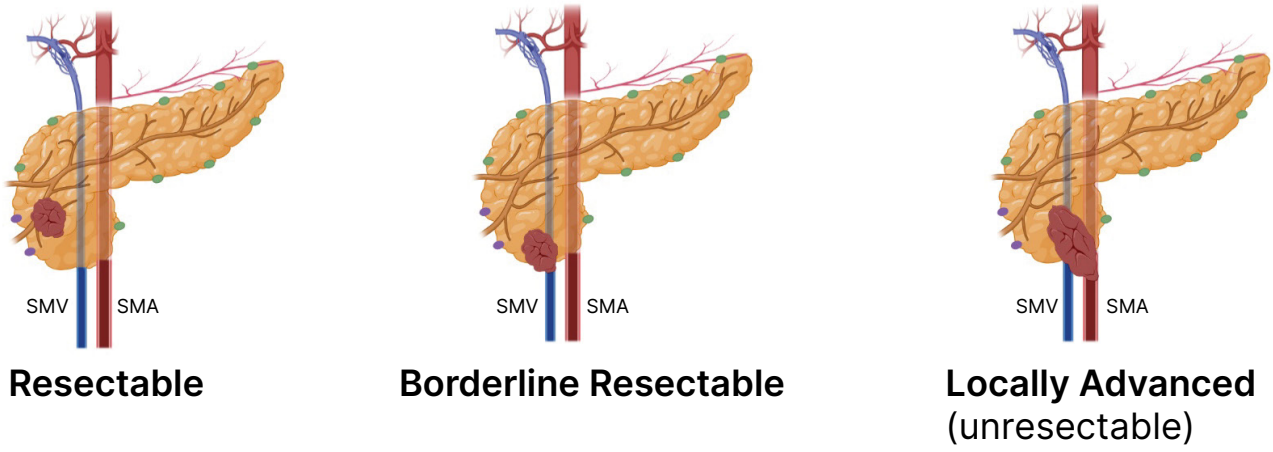


Figure 1. Illustration of resectable, borderline resectable, and locally advanced (unresectable) pancreatic cancers. The figure demonstrates definition based on involvement of the superior mesenteric vein (SMV) or superior mesenteric artery (SMA); *courtesy of Arman Zereshkian, MD and Erica S. Tsang, MD*

reconstructive options or >180 degree vessel involvement or involvement of the duodenum is noted, an LAPC classification is given.[7] Whenever possible, decisions on the treatment of patients with BRPC/LAPC should be made in a multidisciplinary setting involving experienced hepatobiliary surgeons, radiation oncologists, and medical oncologists.[8]

Borderline Resectable Pancreatic Cancer

The optimal treatment approach for patients with BRPC is not yet defined. Based on the currently available evidence, guidelines generally recommend neoadjuvant intent chemotherapy (NAC). The rationale used by clinicians in offering NAC is to increase margin negative (R0) resection rates, to identify patients with rapidly progressive disease who can be spared futile surgery, and to optimize the chance of perioperative therapy, particularly considering that prolonged post-surgical recovery may impede the timely initiation of adjuvant therapy. There is also the potential to improve overall survival (OS) by treating micrometastatic disease. It should be noted that some trials include patients with resectable, BRPC, or LAPC disease, which also adds complexity in interpreting this data.

Optimizing Induction Systemic Therapy Approaches in BRPC

Table 1 provides a summary of recent studies on BRPC. One of the largest phase III multicentre studies to assess the role of neoadjuvant chemoradiation in patients with resectable pancreatic cancer and BRPC was the Dutch PREOPANC trial.[9] In this trial, patients were randomized to receive neoadjuvant gemcitabine with gemcitabine-based radiation (36 Gy in 15 fractions) then 2 weekly doses of gemcitabine followed by surgery and adjuvant gemcitabine for 4 cycles compared to upfront surgery and adjuvant gemcitabine for 6 cycles. An updated analysis published in 2022 demonstrated a difference in the median OS of 1.4 months (15.7 months vs. 14.3 months) favouring the neoadjuvant chemoradiation group despite a hazard ratio (HR) of 0.73. The 5-year OS was higher at 20.5% in the neoadjuvant group compared to 6.5% in the upfront surgery arm. Subgroup analysis of patients with BRPC favoured neoadjuvant chemoradiation. This trial enrolled patients between 2013 and 2017, and since then, the standard of care for adjuvant therapy has changed to include combination regimens. Thus, further trials are required using these newer regimens. It is notable that over half of the patients who participated in this trial were above the age of 65 years and had a World Health Organization (WHO) performance status of 1 or 2. Therefore, this regimen remains applicable in more frail or elderly patients who may be unfit for standard of care adjuvant chemotherapy.

The phase II multicentre ESPAC5 trial compared upfront surgery with three different neoadjuvant treatment arms and included 90 patients with BRPC.[10] These treatment arms included neoadjuvant gemcitabine/capecitabine

Trial Name	Phase	Population	Intervention	Control	Primary Outcome	Sample Size	Region
Neoadjuvant chemotherapy alone							
Prep-02/ JASP05	II/III	BRPC	NAC (gemcitabine + S1) followed by surgery	Upfront surgery	Overall survival	360	South Korea, Japan
NUPAT-01	II	BRPC	NAC (FOLFIRINOX) followed by surgery	NAC (G/N) followed by surgery	R0 resection rate	51	Japan
ESPAC-5	III	BRPC	NAC (FOLFIRINOX or gemcitabine + capecitabine or N-CRT) followed by surgery	Upfront surgery	Recruitment rate and resection rate	90	United Kingdom, Germany
NEOLAP-AIO-PAK-0113	II	LAPC	NAC (FOLFIRINOX)	NAC (G/N)	Surgical conversion rate	130	Germany
Neoadjuvant radiation alone or after neoadjuvant chemotherapy							
A021501	II	BRPC	NAC + Radiation	NAC	Overall survival	126	USA
LAPC-1	II	LAPC	FOLFIRINOX + SBRT	FOLFIRINOX	Overall survival	50	Netherlands
SMART	II	LAPC	Ablative MRI guided radiation	N/A	Gastrointestinal toxicity (secondary endpoint of overall survival)	133	USA, Israel
Neoadjuvant chemoradiotherapy							
LAP07	III	BRPC or LAPC	NAC (gemcitabine) + N-CRT (capecitabine)	NAC (gemcitabine)	Overall survival	449	France
NCT01458717 Trial	II/III	BRPC	N-CRT followed by surgery	Surgery alone	R0 resection rate	58	South Korea
JCOG1106	II	LAPC	NAC (S1) followed by N-CRT	NAC (gemcitabine) followed by N-CRT	Overall survival	100	Japan
JCOG1407	II	LAPC	NAC (FOLFIRINOX)	NAC (gemcitabine + Nab-paclitaxel)	Overall survival	126	Japan

Trial Name	Phase	Population	Intervention	Control	Primary Outcome	Sample Size	Region
JASPAC05	II	BRPC	N-CRT (S1)	N/A	R0 resection rate	50	Japan
CONKO-007	III	BRPC or LAPC	NAC (FOLFIRINOX) + N-CRT	NAC	Tumour resectability	180	Germany
PREOPANC-1	III	Resectable pancreatic cancer or BRPC	N-CRT(gemcitabine) then surgery	Surgery followed by adjuvant gemcitabine	Overall survival	246	Netherlands
NCT01591733	II	BRPC	NAC (FOLFIRINOX) + N-CRT (capecitabine)	N/A	R0 resection rate	48	USA
PREOPANC-2	III	BRPC	N-CRT (gemcitabine) followed by surgery followed by adjuvant gemcitabine	NAC (FOLFIRINOX) followed by surgery	Overall survival	375	Netherlands
Ascott et al.	II	BRPC	N-CRT (nab-paclitaxel)	N-CRT (5-FU or gemcitabine)	Toxicity (secondary endpoint local failure and conversion to resectability)	50	USA
T2212	II	LAPC	NAC (GOFL) + N-CRT (gemcitabine)	NAC (FOLFIRINOX) + N-CRT (gemcitabine)	Progression free survival	55	Taiwan

Table 1. Summary of recent studies informing care of patients with borderline resectable pancreatic cancer/locally advanced pancreatic cancer; *courtesy of Arman Zereshkian, MD and Erica S. Tsang, MD*

Abbreviations: BRPC: Borderline resectable pancreatic cancer; **LAPC:** locally advanced pancreatic cancer; **SOC:** Standard of Care chemotherapy; **USA:** United States of America; **NAC:** Neoadjuvant chemotherapy; **N-CRT:** neoadjuvant chemoradiotherapy

for two cycles, neoadjuvant FOLFIRINOX for 4 cycles, or neoadjuvant chemoradiation (N-CRT) with capecitabine for 5 weeks. All patients who had surgery received adjuvant therapy at the discretion of the treating oncologist. The primary outcomes of the trial were patient recruitment and surgical resection. A 1-year disease-free survival of 33% was noted in the surgery alone arm compared to a 1-year disease-free survival of 59% with neoadjuvant therapies (compiled data). The trial reported that the 1-year OS rate was 39% for immediate surgery compared to 78% with gemcitabine/capecitabine, 84% for those who received FOLFIRINOX and 60% for those who underwent chemoradiation. These differences in 1-year OS were significant (p=0.0028). However, there were no significant differences in R0 resection rates between neoadjuvant chemotherapy and N-CRT. It should be noted that adjuvant gemcitabine was the standard of care regimen at the time of trial design, however, newer standard of care regimens became available near the end of the trial. The results of the ESPAC5 trial demonstrated that NAC or N-CRT resulted in a higher proportion of patients alive at 1 year compared to those who underwent upfront surgery and adjuvant treatment alone. This feasibility trial has demonstrated that neoadjuvant treatment is feasible and possibly effective in the treatment of patients with BRPC, however long-term outcomes have yet to be published.

The recently reported PREOPANC-2 trial was a large phase III trial that involved 375 patients with both BRPC and resectable PDAC that was conducted across 19 centres in the Netherlands.[11] Patients were randomized to 8 cycles of FOLFIRINOX followed by surgery without adjuvant therapy or neoadjuvant gemcitabine with hypofractionated radiotherapy (36 Gy in 15 fractions in cycle 2) followed by surgery then 4 cycles of adjuvant gemcitabine. The trial reported a median OS of 21.9 months in the neoadjuvant FOLFIRINOX arm compared to a median OS of 21.3 months in the chemoradiation arm (HR 0.87, p=0.28). Resection rates were also comparable, at 77% with FOLFIRINOX and 75% with chemoradiation. It is important to note that adjuvant single agent gemcitabine is typically not used unless patients are unfit for combination regimens, thus, the applicability of the chemoradiation arm remains unclear.

Smaller studies have been conducted to compare modern chemotherapy regimens in BRPC. Yamaguchi and colleagues reported results from the phase II NUPAT-01 study that included 51 patients with BRPC. Patients received either FOLFIRINOX for 4 cycles or gemcitabine/nab-paclitaxel for 2 cycles, however, there was no surgery alone arm.[12] In this trial, 15.7% of patients did not undergo surgery. Intention-to-treat analysis demonstrated a 3-year OS of 54.7% and a 5-year OS of 36.6%. In addition, the FOLFIRINOX group demonstrated an improved invasive disease-free survival (iDFS), (p=0.044).. No significant OS difference was observed between the two groups.

Other agents have been used outside of North America for the treatment of pancreatic cancer, such as S-1, which has been used in Asian countries. The Japanese Prep-02/JSAP05 phase II/III trial examined the role of 2 cycles of preoperative gemcitabine combined with S-1 compared to upfront surgery in 364 patients with resectable pancreatic cancers and BRPC[13]. All patients received adjuvant S-1 for 6 months if they had curative resections. The interim results of this trial were presented at the American Society of Clinical Oncology (ASCO) 2019 meeting. The findings demonstrated a median OS of 36.7 months in those who received NAC compared to 26.6 months in those who underwent up-front surgery. The R0 resection rates were similar between the two groups.[14] A recent phase II trial conducted in Japan by Kondo *et al*. assessed the use of 6 cycles of gemcitabine, nab-paclitaxel, and S-1 as NAC for BRPC. This single arm study of 47 patients demonstrated an impressive 86% R0 resection rate with a median OS of 41 months.[15] A subsequent JASPAC05 single arm Japanese phase II trial was conducted in which 41 patients with BRPC received S-1 with concurrent radiotherapy (50.4 Gy in 28 fractions) and then surgery. The R0 resection rate was 63% with a 2-year median OS of 30.8 months.[16]

Can Radiation Augment Responses?

The role of adding radiation after initial induction chemotherapy for BRPC has been explored in a number of studies. Murphy and colleagues reported results from a phase II single centre study of 48 patients with BRPC who received an upfront induction of FOLFIRINOX for 8 cycles. If resolution of vascular involvement was observed, short course chemoradiation (5 Gy x 5 with protons) was administered. If vascular involvement remained, patients underwent long-course chemoradiation (50.4 Gy

in 28 fractions with vascular margin given 58.8 Gy in 28 fractions) with 5-fluorouracil or capecitabine. Results from this small study appeared promising, with an R0 resection observed in 31 patients (65%) and a 2-year OS of 72%.[17]

In a phase II/III trial that was conducted at several Korean centres, Jang *et al*. assessed the role of N-CRT (54 Gy EBRT) with gemcitabine versus upfront surgery and subsequent chemoradiation in patients with BRPC.[18] This study was terminated early owing to a statistically significant benefit of neoadjuvant treatment, at which time 50 patients were accrued out of a planned 110 patients. In the intention to treat (ITT) analysis, the 2-year OS was 41% in the neoadjuvant group compared to 26% in the upfront surgery group. The median OS was significantly longer in the N-CRT arm (21 months) vs. surgery and subsequent CRT (12 months).[19] Of note, this was a small study with 50 enrolled patients, which had provided the impetus for further trials assessing the use of N-CRT as opposed to adjuvant CRT.

Stereotactic body radiation therapy (SBRT) has been touted as being able to deliver a higher biological effective dose (BED) in a shorter time frame. Early small studies of SBRT in BRPC have been reported to allow approximately 50% of patients to proceed to surgical resection.[20,21] Given these results, SBRT was investigated in the larger Alliance A021501 phase II trial. In this trial, 126 patients with BRPC were randomized to 8 cycles of preoperative FOLFIRINOX or to 7 cycles of FOLFIRINOX followed by SBRT (33–40 Gy in 5 fractions) or to hypofractionated image-guided radiation (25 Gy in 5 fractions).[19] If disease progression was not observed, patients underwent surgical resection. With a primary endpoint of 18-month OS, the trial was powered to compare the 18-month OS with a historical reference of 50% survival at 18 months, rather than comparing between the two arms. At the interim analysis, only 33% of patients had an R0 resection in arm 2 (combination arm), thus, this arm was closed early. Patient accrual continued for arm 1 (FOLFIRINOX alone). The findings indicated an 18-month OS of 66.7% in the chemotherapy alone arm compared to 47.3% in the radiation arm. It should be noted that the median carbohydrate antigen 19-9 level was higher in the radiation arm (a median of 260 in the radiation arm compared to a median of 167 in the chemotherapy arm). A lower percentage of patients in the radiation arm underwent surgical resection (35%) compared to 49% after FOLFIRINOX alone, which may have impacted the primary endpoint. This is also thought to potentially reflect the heterogeneity of enrolling centres, which may not all have been high volume pancreatic cancer centres. Overall, this study solidified the role of FOLFIRINOX as a neoadjuvant treatment regimen in BRPC.

Locally Advanced Pancreatic Cancer

Table 1 provides a summary of recent studies on LAPC. FOLFIRINOX remains the most commonly used treatment regimen for patients with LAPC, despite the lack of randomized prospective phase III data. The JCOG1407 study compared FOLFIRINOX with gemcitabine/nab-paclitaxel in 126 patients with LAPC.[22] This trial reported a higher efficacy compared to historical numbers with gemcitabine alone, with a 1-year OS of 77.4% and 82.5% in the FOLFIRINOX and gemcitabine/nab-paclitaxel arms, respectively. The median PFS was 11.2 months and 9.4 months in the FOLFIRINOX and gemcitabine/nab-paclitaxel arms, respectively. In a patient-level meta-analysis, Suker and colleagues examined 13 studies which included a total of 355 patients with LAPC. The percentage of patients who also went on to receive radiotherapy ranged from 31% to 100%.[23] Overall, FOLFIRINOX appeared to have a longer median OS compared to gemcitabine.

Other gemcitabine-based regimens have been studied. Kunzmann and colleagues reported results from the NEOLAP-AIO-PAK-0113 phase II trial that included patients with LAPC, in which patients received 2 cycles of gemcitabine and nab-paclitaxel. If no evidence of disease progression was observed, patients would then be randomized to an additional 2 cycles of gemcitabine/nab-paclitaxel or to 4 cycles of FOLFIRINOX. No difference was observed in the primary endpoint of surgical conversion rate (complete macroscopic tumour resection), at 35.9% in the gemcitabine/nab-paclitaxel group vs. 43.9% in the sequential FOLFIRINOX group (p=0.38). No significant differences in overall survival were noted between the two strategies (median OS of 18.5 months vs. 20.7 months respectively, p=0.53).[24] Gemcitabine alone is typically not used given the low conversion rates to resectability. It is reserved for patients who would not otherwise tolerate combination chemotherapy.

Additional combination chemotherapeutic regimens outside of FOLFIRINOX and gemcitabine have also been investigated. Arscott and colleagues recruited 50 patients with BRPC

and LAPC. Of these, 28 patients received concurrent nab-paclitaxel with radiation (52.5 Gy total) and 22 patients received standard chemoradiation (54.5 Gy total).[25] Toxicity was a primary endpoint, with toxicities being similar between the two groups. A higher proportion of patients (9 of 28; 32%) went on to surgery in the nab-paclitaxel arm compared to the standard chemoradiation (3 of 22; 14%). The Taiwan Cooperative Oncology Group T2212 trial used gemcitabine, oxaliplatin, 5-FU/leucovorin (GOFL) or FOLFIRINOX as the induction regimen, then patients underwent 5-FU or gemcitabine-based chemoradiation (5040 cGy/28 fractions).[26] No differences in PFS or OS were observed between these two arms.

Role of Radiation in LAPC

Similar to BRPC, the addition of radiation to chemotherapy has also been studied. The goal of radiation therapy in these circumstances is to achieve local control. In a rapid autopsy series of patients with stage III and IV PDAC, 30% of them died from locally destructive disease, namely tumour infiltration to nearby structures.[27] Clinically, this manifests as epigastric and back pain, gastric outlet obstruction, bleeding, and obstructive jaundice. Local control through radiation therapy is meant to prevent these types of complications and to improve outcomes.

In the LAP-07 trial, patients with LAPC were initially randomized to either gemcitabine alone or gemcitabine with erlotinib for four cycles.[28] If no evidence of progression was observed after induction chemotherapy, patients were randomized to either chemoradiotherapy with capecitabine (54 Gy of EBRT with capecitabine at 1600 mg/m^2 per day) or an additional 2 months of gemcitabine alone. The primary endpoint was OS. The trial was stopped early (accrual reached 442 out of a planned 820 patients) owing to futility at the interim analysis in which no difference with chemoradiotherapy was found (or with erlotinib use). The ITT analysis demonstrated no difference in OS between induction chemotherapy regimens (median OS of 13.6 months with gemcitabine alone and 11.9 months with gemcitabine/erlotinib; HR 1.19). An ITT analysis of the second randomization comparing chemoradiation with chemotherapy also showed no difference in OS (15.2 months and 16.5 months respectively; HR 1.03). Some radiation deviations were noted (18% of patients experienced major deviations, 50% of patients experienced minor deviations), although this did not appear to impact survival outcomes.

This concept of chemoradiation post induction chemotherapy was further studied in the CONKO-007 phase III trial in which patients with LAPC received 3 months of induction chemotherapy with either FOLFIRINOX or single agent gemcitabine. If no progression was observed, patients were then randomized to continue chemotherapy for an additional 3 months or to receive chemoradiation (50.4 Gy) with gemcitabine. The primary endpoint was OS, but was later changed to R0 resection rate due to slow patient accrual. Over the course of 8 years, 525 patients were enrolled, of which 335 were randomized. Among the 122 patients who underwent surgery, R0 resection rate was higher in the chemoradiation arm at 69% vs. 50% in the gemcitabine alone arm. However, no statistically significant difference was noted when comparing R0 resection rates among all randomized patients (25% in the chemoradiation arm vs. 18% in the gemcitabine alone arm, p=0.11). No differences in PFS or OS were observed.[29]

The JCOG1106 phase II trial published by Ioka *et al*. included patients with LAPC and assessed the role of upfront chemoradiation compared to induction chemotherapy followed by radiation. Patients in arm A received chemoradiotherapy with S-1, whereas patients in arm B received gemcitabine for 12 weeks followed by radiotherapy with S-1. The results of this trial were reported to favour chemoradiotherapy alone. The 2 year median OS was longer in arm A vs arm B (36.9% vs 18.9%, respectively),[30] although single agent gemcitabine is now rarely used in this setting.

Novel Radiation Techniques in LAPC

Newer technologies, such as SBRT, have facilitated the precise delivery of high dose radiation to treat LAPC. Early small studies have demonstrated high local control rates with SBRT ranging from 89%–100%.[31–33] Intensity modulated radiation therapy (IMRT) and image guided techniques have been explored to allow dose escalation in certain areas of the tumour to maximize the treatment effect and minimize toxicities. Rudra and colleagues employed adaptive magnetic resonance imaging-guided radiation therapy, including conventional fractionation, hypofractionation, and SBRT, to treat 44 patients with unresectable LAPC.[34] Patients who received high-dose

radiation were found to have a longer 2-year OS compared to those who received standard doses (49% vs. 30%, respectively, p=0.03). In another study, Krishnan *et al*. reviewed the outcomes of 200 patients with LAPC who were treated with induction chemotherapy followed by chemoradiation in which 24% of them received dose-escalated IMRT.[35] Those who received a BED >70 Gy had a longer OS (median of 17.8 months vs. 15 months, p=0.03), with no significant differences in toxicity observed.

Crane and colleagues used high-dose hypofractionated radiation (98 Gy BED) to treat 119 patients with LAPC in a single centre cohort study after a median of 4 months of induction chemotherapy.[36] The 2-year OS, from the time of ablative radiation, was 38%, and the median OS from diagnosis was 26.8 months. Locoregional failure occurred in 32.8% of patients at the two-year mark. Given these promising results, further studies using ablative radiation therapy in patients with LAPC are warranted.

A number of novel radiation-based therapies are currently being employed in the treatment of BRPC/LAPC. These include electrochemotherapy, proton and carbon ion radiation, and electroporation. A few small phase I/II trials have assessed these novel treatments, and more trials are needed to clarify their role in patients with BRPC/LAPC.

Emerging Role of Cancer Vaccines

There is much excitement in the realm of cancer vaccines, with the promise of impacting the immunologically "cold" tumour microenvironment in PDAC. Early favourable results with a personalized neoantigen vaccine in the resectable PDAC setting with long-term survivors has now led to a prospective phase III trial, for which we eagerly await results.[37]

The phase I/II LAPC-2 trial recruited 38 patients with LAPC who had received induction chemotherapy with FOLFIRINOX.[38] They were then treated with SBRT (40 Gy) and 6 biweekly vaccinations of heat-killed myobacterium (IMM 101). There were 13 grade 3 events and one grade 5 event, which were not related to the IMM-101 vaccination. The median OS was 19 months, and 21% of patients were able to undergo resection.

One of the largest trials to date in BRPC or LAPC was the HyperAcute-Pancreas-Immunotherapy (HAPa) phase III study.[39] This vaccine was made of allogeneic pancreatic cancer cells expressing the murine alpha(1,3) GT gene, with the goal of increasing immunogenicity. Patients with BRPC or LAPC received upfront FOLFIRINOX or gemcitabine/nab-paclitaxel followed by either HAPa immunotherapy or chemoradiation. There was no significant difference in the median OS (14.9 months vs 14.3 months, respectively), progression free survival, or grade 3 adverse events. There was also no difference in terms of conversion to resectability.

Conclusions and Future Directions

Treatment of patients with BRPC and LAPC continues to evolve owing to advancements in drug discovery, surgical procedures, and radiation techniques. A number of active clinical trials are currently underway to optimize systemic therapy regimens and to elucidate the role of radiation in this setting (**Table 2**). Novel radiation techniques, including proton radiotherapy, cyberknife, and ultrasound, are under investigation. The addition of immunotherapy in the neoadjuvant setting is also being explored. Taken together, these novel approaches and emerging techniques hold substantial promise to improve survival outcomes in patients with BRPC and LAPC.

Registration ID	Phase	Population	Intervention	Control	Primary outcome	Expected sample size	Region
NCT02676349	II RCT	BRPC	NAC (FOLFIRINOX) + CRT	NAC (FOLFIRINOX)	R0 resection rate	130	France
NCT05634564	II single arm open label	BRPC	Gemcitabine + tislelizumab + nab paclitaxel + radiation	N/A	Overall response rate	62	China
NCT05083247 (STEREOPAC)	II RCT	BRPC	NAC (FOLFIRINOX) x 8 cycles	NAC (FOLFIRINX) x 6 cycles followed by SBRT	Disease free survival and R0 resection rate	256	Belgium
NCT05415917	II open label	Resectable or LAPC or BRPC	NAC followed by surgery gemcitabine + capecitabine	NAC followed by surgery and observation	Safety	75	USA
NCT03777462	II	BRPC	N-CRT	NAC alone	Overall survival	150	China
NCT03983057	III	BRPC or LAPC	NAC (FOLFIRINOX) + PD-1 antibody	NAC (FOLFORINOX)	Progression free survival	830	China
NCT03563248	II	BRPC or LAPC	NAC + losartan + nivolumab + SBRT	NAC + SBRT	R0 resection rate	168	USA
NCT04390399	II open label	LAPC or metastatic pancreatic cancer	SOC Chemotherapy + aldoxorubicin + PD-L1 therapy	SOC chemotherapy	Progression free survival	328	USA
NCT02598349	II	BRPC or LAPC	N-CRT (proton radiotherapy)	N/A	Overall survival	60	USA
NCT03377491	III	LAPC	N-CRT (Tumour treating fields + chemotherapy)	SOC chemotherapy	Overall survival	556	Multicentre (Multiple Countries)
NCT02539537 (NEOPAN)	III	LAPC	FOLFIRINOX	Gemcitabine	Progression free survival	171	France
NCT03899636	III	LAPC	FOLFIRINOX + Irreversible electroporation (Nanoknife)	FOLFIRINOX	Overall survival	528	USA
NCT04986930 (SABER)	II	LAPC	NAC (FOLFIRINOX) + SBRT	NAC (FOLFIRINOX)	Overall survival	92	South Korea

Registration ID	Phase	Population	Intervention	Control	Primary outcome	Expected sample size	Region
NCT03941093 (LAPIS)	III	LAPC	NAC + pamrevlumab	NAC	Overall survival	284	Multicentre (Multiple Countries)
NCT04617821	III	BRPC	NAC (mFOLFIRINOX)	NAC (gemcitabine + Nab-paclitaxel)	Overall survival	300	China
NCT03257033	III	LAPC	NAC + radiation followed by Intra-arterial gemcitabine	NAC + radiation	Overall survival	320	USA, Belgium
NCT05466799	II	LAPC	FOLFIRINOX+ Oncosil™	FOLFIRINOX	Safety + Local disease control rate	80	Belgium, Italy, Spain, United Kingdom
NCT04821284	I/II	LAPC or metastatic pancreatic cancer	SOC chemotherapy + sonoporation	SOC chemotherapy	Progression free survival	120	USA, Norway
NCT01585805	I/II	LAPC or metastatic pancreatic cancer	Gemcitabine + cispatin + veliparib	Gemcitabine + cispatin	Optimal dose + response rate	107	USA, Canada, Israel
NCT05851924	II	BRPC/LAPC	NALIRIFOX + ablative radiation therapy	N/A	Event free survival	60	USA
NCT04570943 (GABRINOX-ART)	II	LAPC	NAC (G/N) followed by FOLFIRINOX followed by MRI guided radiotherapy	N/A	Progression Free Survival	103	France
NCT05825066	II	BRPC/LAPC	NAC	N/A	R0 resection rate	64	USA
NCT02839343	II	BRPC	NAC + radiation	NAC	Overall survival	126	USA, Canada

Table 2. Ongoing Phase II/III trials in patients with borderline resectable pancreatic cancer or locally advanced pancreatic cancer with >60 patients; *courtesy of Arman Zereshkian, MD and Erica S. Tsang, MD*

Abbreviations: BRPC: Borderline resectable pancreatic cancer, **LAPC:** locally advanced pancreatic cancer, **SOC:** Standard of Care chemotherapy, **USA:** United States of America, **NAC:** Neoadjuvant chemotherapy, **N-CRT:** neoadjuvant chemoradiotherapy

Correspondence

Erica S. Tsang, MD
Email: erica.tsang@uhn.ca

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