

Canadian Oncology Today

Volume 2, Issue 3

Treatment of dMMR Metastatic Colorectal Cancer in 2025

Renata D'Alpino Peixoto, MD, PhD
Thiago Miranda do Amaral, MD

First-line Treatment Selection for Advanced Unresectable Biliary Tract Cancer

Arwa Ahmed Abdelrahim, MD
Rachel Goodwin, MD

Original Research: Biomarker Testing in a Canadian Centre for Patients with Non-small Cell Lung Cancer: Assessing Residual Risks

Yunting Liu, Steven Shen, Manav Shukla, Janet Malowany, Shaheed Hakim, Zared Aziz, David N. Parente, Victoria Cheung, Suneil Khanna, Yoo-Joung Ko, Wondwossen Kidanewold, Michael A. Ko, Kelsie L. Thu, Ju-Yoon Yoon

Current Issues in the Management of Sporadic Non-clear Cell Renal Cell Carcinoma (Non-ccRCC)

Mariam Jafri, MBChB (Hons), MRCP(UK), BMedSc, MSc, Ph.D

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

Fall 2025

Editorial Board



Normand Blais, MD

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



Christine Brezden-Masley, MD, PhD, FRCPC

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



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

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



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

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

Table of Contents

Treatment of dMMR Metastatic Colorectal Cancer in 2025	4
Renata D'Alpino Peixoto, MD, PhD Thiago Miranda do Amaral, MD	
First-line Treatment Selection for Advanced Unresectable Biliary Tract Cancer.....	10
Arwa Ahmed Abdelrahim, MD Rachel Goodwin, MD	
Original Research: Biomarker Testing in a Canadian Centre for Patients with Non-small Cell Lung Cancer: Assessing Residual Risks	20
Yunting Liu, Steven Shen, Manav Shukla, Janet Malowany, Shaheed Hakim, Zared Aziz, David N. Parente, Victoria Cheung, Suneil Khanna, Yoo-Joung Ko, Wondwossen Kidanewold, Michael A. Ko, Kelsie L. Thu, Ju-Yoon Yoon	
Current Issues in the Management of Sporadic Non-clear Cell Renal Cell Carcinoma (Non-ccRCC)	27
Mariam Jafri, MBChB (Hons), MRCP(UK), BMedSc, MSc, Ph.D	

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

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

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

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

Canadian Oncology Today is an open access journal, which means all its content is freely available without charge. Users are permitted to copy and redistribute the material in any medium or format for any noncommercial purpose, provided they cite the source.

© 2025 Canadian Oncology Today. Licensed under CC BY-NC-ND 4.0.
To learn more about our policies please visit canadianoncologytoday.com.

About the Authors



Renata D'Alpino Peixoto, MD, PhD

Dr. Peixoto is a Clinical Assistant Professor at the University of British Columbia and a medical oncologist at BC Cancer, Vancouver Centre, specializing in gastrointestinal cancers. She completed her PhD in Oncology Universidade Nove de Julho, focusing on pancreatic cancer. She received her medical degree at Faculdade de Ciencias Medicas da Santa Casa de Sao Paulo in 2006, completed her Internal Medicine at Faculdade de Medicina da Universidade de Sao Paulo and Medical Oncology Residency at Hospital Sirio Libanes, Sao Paulo, Brazil. She subsequently undertook a Gastrointestinal Oncology fellowship at BC Cancer-Vancouver from 2012 to 2014. Her research interests include molecular studies, outcomes-based research, and clinical trials in gastrointestinal cancers.

Affiliations: B.C. Cancer Agency, Vancouver, B.C.



Thiago Miranda do Amaral, MD

Dr. Thiago Miranda do Amaral completed his residency in Medical Oncology at the Superior School of Health Sciences of Brasília and holds a master's degree from the Instituto Sírio-Libanês de Ensino e Pesquisa. He is currently a clinical-research Fellow in Gastrointestinal Oncology at BC Cancer, Vancouver.

Affiliations: B.C. Cancer Agency, Vancouver, B.C.

Treatment of dMMR Metastatic Colorectal Cancer in 2025

Renata D'Alpino Peixoto, MD, PhD
Thiago Miranda do Amaral, MD

Introduction

Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), accounting for approximately 4–5% of cases, represents a distinct molecular subgroup with unique therapeutic implications.¹ These malignancies are characterized by a high mutational burden and increased immune cell infiltration, making them particularly responsive to immune checkpoint inhibitors (ICI).² Conversely, this subgroup tends to be less sensitive to traditional chemotherapy.³

ICI in mCRC

Programmed cell death protein 1 (PD-1) blockade initially demonstrated success in many refractory malignancies. However, in one of the early studies, only one out of 33 patients with mCRC responded to treatment.⁴ Notably, this patient had a dMMR tumour. This pivotal observation led to extensive clinical trials evaluating PD-1 inhibitors, either alone or in combination with a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor (ipilimumab), in dMMR mCRC.^{5–9} These studies ultimately established immunotherapy as the cornerstone of treatment for this molecular subtype.

As with most oncology drugs, ICI were initially studied in refractory dMMR mCRC. Following remarkable responses and the emergence of long-term survivors, their efficacy was subsequently evaluated in the first-line setting, leading to a paradigm shift in the management of dMMR mCRC. The first major clinical trial to draw global attention to immunotherapy in mCRC was the non-randomized Phase II KEYNOTE-016 study.⁵ This trial evaluated the efficacy of pembrolizumab (PD-1 inhibitor; 10 mg/kg every 14 days) in three small patient cohorts: 10 patients with dMMR mCRC, 18 with proficient mismatch

repair (pMMR) mCRC, and 7 with dMMR non-CRC malignancies. Among patients with dMMR mCRC, the overall response rate (ORR) was 40%, and the 20-week immune-related progression-free survival (PFS) rate was 78%. In contrast, no responses were observed in pMMR mCRC, and only 11% of patients remained progression-free at 20 weeks.

Nivolumab, another PD-1 inhibitor, demonstrated significant activity as monotherapy in one of the Phase II CheckMate-142 trial cohorts. In this cohort, 74 patients with dMMR mCRC, including 53 who had received at least one prior line of systemic therapy, were treated with nivolumab (3 mg/kg every 2 weeks). The study reported an ORR of 31.1% and a disease control rate (DCR) of 69%, with eight patients experiencing responses lasting over a year.¹⁰

Another cohort within the CheckMate-142 trial explored the combination of nivolumab (3 mg/kg) with ipilimumab (1 mg/kg) administered every 3 weeks for four doses, followed by nivolumab monotherapy every 2 weeks in 119 patients with refractory dMMR mCRC. This combination achieved an ORR of 55%.¹¹ The study further expanded to include a cohort of 45 patients, evaluating the dual ICI regimen of nivolumab and ipilimumab as first-line therapy in dMMR mCRC. Unlike the refractory setting, ipilimumab was administered at 1 mg/kg every 6 weeks, resulting in an ORR of 69% and a DCR of 84%.⁷ While direct comparisons between these cohorts are challenging, two noteworthy observations emerge. The addition of ipilimumab to nivolumab appeared to enhance the ORR, suggesting a synergistic effect in dMMR mCRC. Additionally, the modified dosing schedule of ipilimumab (1 mg/kg every 6 weeks) in the first-line setting was associated with fewer severe adverse events, indicating a more tolerable safety profile.

The multicenter KEYNOTE-177 trial was the first Phase III study, enrolling 307 participants, to demonstrate a statistically significant and clinically meaningful improvement in PFS with

pembrolizumab compared to investigator's choice of chemotherapy in the first-line treatment of MSI-H/dMMR mCRC. At final analysis, the median PFS was 16.5 months with pembrolizumab versus 8.2 months with chemotherapy (hazard ratio [HR]: 0.59). The ORR was also higher in the pembrolizumab arm (45.1% vs. 33.1%), with responses being more durable, and therapy was associated with a more favourable toxicity profile. Although the median overall survival (OS) was numerically longer with pembrolizumab (not reached vs. 36.7 months with chemotherapy), it did not reach statistical significance. This may have been influenced by a high crossover rate (60%) from chemotherapy to immunotherapy.¹²

Therapy Resistance

An important finding of the KEYNOTE-177 trial was that approximately one-third of patients in the pembrolizumab arm experienced disease progression within the first three months of treatment. The survival curves showed an early crossing, suggesting that a subset of patients initially fared better on chemotherapy than on pembrolizumab monotherapy. This raises the question of whether combining chemotherapy with ICI could help overcome this early resistance. This hypothesis is currently being tested in ongoing Phase III trials, such as the COMMIT study¹³, which is investigating atezolizumab (an anti-programmed cell death ligand 1 [PD-L1] monoclonal antibody) as monotherapy versus a combination of FOLFOX (folinic acid, fluorouracil, and oxaliplatin), bevacizumab, and atezolizumab as first-line therapy for dMMR mCRC.

Until recently, the only evidence suggesting that the addition of ipilimumab (anti-CTLA-4) to an anti-PD-1 agent could partially mitigate primary resistance to single-agent PD-1 blockade came from the first-line cohort of the Phase II CheckMate-142 trial.¹⁰ However, given the non-randomized nature of this trial, it was not possible to definitively conclude that dual ICI therapy was superior to PD-1 blockade alone.

This paradigm has now shifted with the recent data publication of the Phase III CheckMate 8HW trial, marking a significant milestone in the evolution of treatment strategies for dMMR mCRC.^{14,15} In this study, patients with dMMR mCRC, irrespective of the number of prior lines of therapy, were randomly assigned in a 2:2:1 ratio to one of the following treatment arms: **1)** nivolumab 240 mg plus ipilimumab 1 mg/kg

every three weeks for four doses, followed by nivolumab 480 mg every four weeks (n=353); **2)** nivolumab 240 mg every two weeks for six doses, followed by nivolumab 480 mg every four weeks (n=354); or **3)** the investigator's choice of doublet chemotherapy (FOLFOX or FOLFIRI [folinic acid, fluorouracil, and irinotecan]), with or without bevacizumab or cetuximab (n=132). The dual independent primary endpoints were PFS for nivolumab plus ipilimumab versus chemotherapy (in the first-line setting) and PFS for nivolumab plus ipilimumab versus nivolumab monotherapy (across all lines of therapy) in patients with dMMR mCRC.

A total of 303 patients who had not previously received systemic treatment for their metastatic disease were included in the first phase of the analysis. The median PFS was not reached in the ICI arm, compared to 5.8 months in the chemotherapy arm (HR: 0.21; p<0.0001). Additionally, the incidence of grade 3–4 treatment-related adverse events (TRAEs) was lower in the ICI arm than in the chemotherapy group.

In the second phase of the analysis, 707 patients were randomized to receive either nivolumab plus ipilimumab or nivolumab monotherapy, regardless of prior lines of therapy. The combination of both ICIs resulted in a significant improvement in median PFS, which was not reached in the combination arm compared to 39.3 months in the nivolumab monotherapy arm (HR: 0.62, p=0.0003). Additionally, the ORR was 71% in the dual ICI arm compared to 58% in the nivolumab monotherapy arm, with 30% and 28% having complete responses, respectively. However, those benefits were accompanied by a slightly higher incidence of grade 3 or 4 TRAEs (22% vs. 14%). Further follow-up of the CheckMate 8HW trial is eagerly anticipated, particularly regarding OS outcomes. A summary of these findings and key results from other pivotal trials in MSI-H/dMMR mCRC is provided in **Table 1**.

In nearly all clinical trials evaluating ICIs, the therapeutic benefit of immunotherapy has remained consistent across various subgroups, irrespective of *BRAF* or *RAS* mutation status, the presence of Lynch syndrome, or the sites of metastases. This consistency underscores the broad applicability of ICIs in the treatment of dMMR mCRC, independent of underlying molecular or clinical characteristics.

Study (Year)	Phase	N	Population	Arms	Median OS	Median PFS	ORR	Grade 3-4 TRAEs
KEYNOTE-016 Cohort A (CRC) (2015) ^{5,22}	II	41	Refractory MSI-H/dMMR CRC	PEMBRO 10 mg/kg q14d	80.8 (95% CI: 33.2-NE)	38.8 (95% CI: 8.1-NE)	56.1%	41%
CheckMate-142 First-line Cohort (2021) ⁷	II	45	Untreated MSI-H/dMMR mCRC	IPI 1 mg/kg q6w + NIVO 3 mg/kg q2w	Not reached	Not reached	69%	22%
CheckMate-142 Refractory Cohort (2017) ¹⁰	II	74	dMMR/MSI-H mCRC with ≥1 prior lines of therapy	NIVO 3 mg/kg q2w	Not reached	14.3 mo; 95% CI: 4.3 – NE	31.1%	21%
KEYNOTE-177(2022) ¹²	III	307	Untreated MSI-H/dMMR mCRC	PEMBRO 200 mg q3w vs. CT	NR vs 36.7 mo; HR: 0.74; 95% CI: 0.53-1.03; P= 0.036	16.5 mo vs 8.2; HR: 0.59; 95% CI: 0.45-0.79	45% vs. 33%	21.6% vs. 67.1%
CheckMate 8HW NIVO + IPI vs. CT (2024) ¹⁴	III	303	MSI-H/dMMR mCRC	IPI 1 mg/kg + NIVO 240 mg q3w for 12 w followed by NIVO 480 mg q4w vs. CT	Not reported	NR (95% CI: 34.3-NE) vs. 6.2 mo (95% CI: 4.7-9.0)	Not reported	23% vs. 48%
CheckMate 8HW NIVO + IPI vs. NIVO (2025) ¹⁵	III	707	MSI-H/dMMR mCRC	IPI 1 mg/kg + NIVO 240 mg q3w for 12 w followed by NIVO 480 mg q4w vs. NIVO 240 mg q2w for 12 w followed by NIVO 480 mg q4w	Not reported	NR vs. 39.3 mo; HR: 0.62; 95% CI: 0.48-0.81; P=0.0003	71% vs. 58%	22% vs. 14%

Table 1. Key results from pivotal ICI trials in MSI-H/dMMR mCRC; courtesy of Renata D'Alpino Peixoto, MD, PhD, and Thiago Miranda do Amaral, MD.

Abbreviations: CI: confidence interval; CT: investigator's choice of chemotherapy; **dMMR:** deficient mismatch repair; **DOR:** duration of response; **HR:** hazard ratio; **IPI:** ipilimumab; **mCRC:** metastatic colorectal cancer; **mo:** months; **MSI-H,** microsatellite instability-high; **ne:** not evaluable; **NIVO:** nivolumab; **NR:** not reached; **OS:** overall survival; **PD-1:** programmed cell death protein 1; **PEMBRO:** pembrolizumab; **PFS:** progression-free survival; **TRAEs:** treatment-related adverse events; **w:** weeks.

Remaining Questions for Immunotherapy use in dMMR mCRC

Several unanswered questions remain regarding the optimal use of ICIs in dMMR mCRC, including the ideal treatment duration. In pivotal clinical trials, patients with mCRC who do not experience disease progression or unacceptable toxicities typically receive ICIs for up to two years, after which treatment is discontinued. An observational cohort study involving 757 patients with dMMR mCRC treated with immunotherapy found that continuing treatment beyond two years did not improve OS. Furthermore, for patients who achieved a complete response, discontinuation of therapy after one year was not associated with any detrimental impact on OS.¹⁶

Another important consideration is the optimal therapy sequencing in patients with both dMMR and *BRAF*-mutated tumours. Approximately one-third of dMMR mCRC cases harbour the *BRAF* V600E mutation, often arising due to *MLH1* promoter hypermethylation. Despite the recent positive results from the Phase III BREAKWATER trial, which demonstrated that adding encorafenib and cetuximab to FOLFOX in the first-line setting improved ORR and OS compared to standard chemotherapy in patients with pMMR *BRAF* V600E-mutated mCRC, most oncologists would prioritize ICIs for patients who are also dMMR.¹⁷ This preference is driven by the efficacy of ipilimumab plus nivolumab, which has been shown to induce complete responses in 30% of patients and provide durable responses. In such scenarios, the combination of FOLFOX, cetuximab, and encorafenib, as investigated in the BREAKWATER trial, could be considered in the second-line setting. Alternatively, encorafenib plus cetuximab, in alignment with the findings from the BEACON trial, may also represent a reasonable treatment option.¹⁸ Nonetheless, future clinical trials evaluating the role of combining *BRAF* inhibitors with cetuximab or panitumumab and ICIs would be highly informative.

Another unresolved question pertains to the potential benefit of adding an anti-CTLA-4 agent in patients who have progressed on single-agent anti-PD-1 or anti-PD-L1 therapy. There is a strong biological rationale supporting this approach. CTLA-4 primarily regulates T-cell activation during the initial immune response, whereas PD-1/PD-L1 signaling predominantly suppresses T-cell activity

within the tumour microenvironment. Combining anti-CTLA-4 with anti-PD-1 ICI may help overcome adaptive resistance mechanisms that emerge with anti-PD-1 monotherapy, thereby restoring immune activity against tumour cells. Some case reports have documented instances in which anti-PD-1 therapy had previously failed, but therapy response was recorded when ipilimumab was added to the regimen.^{19,20}

Another critical issue is the potential for false-positive dMMR results in local laboratory testing. Studies have indicated that up to 60% of patients who exhibit disease progression on their first imaging evaluation during immunotherapy were subsequently found to be false-positive for dMMR based on local laboratory assessments. This highlights the necessity of centralized confirmation of MMR status to ensure accurate patient selection for immunotherapy.²¹

Future Directions

Several novel strategies are currently under investigation to enhance the efficacy of ICIs in dMMR mCRC. These include combinations of ICIs with other ICIs, cytotoxic chemotherapy, monoclonal antibodies, targeted therapies, or novel agents. Additionally, ICIs are being incorporated into earlier stages of colorectal cancer treatment and are undergoing evaluation in neoadjuvant and adjuvant settings.

At present, pembrolizumab is approved across Canada for the first-line treatment of dMMR mCRC. However, while the approval of ipilimumab and nivolumab in this setting appears likely, it remains uncertain. Despite the clear clinical benefits associated with the addition of ipilimumab to nivolumab, this does need to be carefully balanced against increased toxicity and costs.

Correspondence

Renata D'Alpino Peixoto, MD, PhD

Email: renata.peixoto@bccancer.bc.ca

Financial Disclosures

R.P.: None declared.

T.A.: None declared.

References

- Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: A Pooled Analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res*. 2014;20(20):5322–30.
- Llosa NJ, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov*. 2015;5(1):43–51.
- Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med*. 2003;349(3):247–57.
- Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010;28(19):3167–75.
- Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509–20.
- André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207–18.
- Lenz HJ, Van Cutsem E, Luisa Limon M, Wong KYM, Hendisz A, Aglietta M, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the Phase II CheckMate 142 study. *J Clin Oncol*. 2022;40(2):161–70.
- Le DT, Kim TW, Van Cutsem E, Geva R, Jäger D, Hara H, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. *J Clin Oncol*. 2020;38(1):11–9.
- André T, Elez E, Lenz HJ, Jensen LH, Touchefeu Y, Van Cutsem E, et al. Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial. *Lancet*. 2025;405(10476):383–95.
- Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18(9):1182–91.
- Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773–9.
- Diaz LA, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol*. 2022;23(5):659–70.
- Overman MJ, Yothers G, Jacobs SA, Sanoff HK, Cohen DJ, Guthrie KA, et al. Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study: A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or . *J Clin Oncol*. 2024;42(3_suppl):TPS231–TPS231.
- André T, Elez E, Van Cutsem E, Jensen LH, Bennouna J, Mendez G, et al. Nivolumab plus ipilimumab in microsatellite-instability-high metastatic colorectal cancer. *N Engl J Med*. 2024;391(21):2014–26.
- André T, Elez E, Lenz HJ, Jensen LH, Touchefeu Y, Van Cutsem E, et al. Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial. *Lancet*. 2025;405(10476):383–95.
- Margalit O, Stemmer A, Chapin WJ, Shacham-Shmueli E, Kopetz S, Andre T, et al. Duration of immunotherapy in dMMR/MSI-H metastatic colorectal cancer patients. *Eur J Cancer*. 2024;212:114336.
- Kopetz S, Yoshino T, Van Cutsem E, Eng C, Kim TW, Wasan HS, et al. Encorafenib, cetuximab and chemotherapy in BRAF-mutant colorectal cancer: a randomized phase 3 trial. *Nat Med*. 2025;31(3):901–8.
- Tabernero J, Grothey A, Van Cutsem E, Yaeger R, Wasan H, Yoshino T, et al. Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. *J Clin Oncol*. 2021;39(4):273–84.
- Hamre TR, Stougaard JK, Havelund BM, Jensen LH, Hansen TF. Re-exposure to immunotherapy in metastatic colon cancer: A case report. *Clin Case Reports*. 2021;9(6):e04349.
- Das S, Allen A, Berlin J. Immunotherapy after immunotherapy: response rescue in a patient with microsatellite instability-high colorectal cancer post-pembrolizumab. *Clin Colorectal Cancer*. 2020;19(2):137–40.
- Cohen R, Hain E, Buhard O, Guilloix A, Bardier A, Kaci R, et al. Association of primary resistance to immune checkpoint inhibitors in metastatic colorectal cancer with misdiagnosis of microsatellite instability or mismatch repair deficiency status. *JAMA Oncol*. 2019;5(4):551.
- Bever KM, Durham JN, Qi H, Azad NS, Laheru D, Fisher GA, et al. 10-year follow up of a phase 2 clinical trial of pembrolizumab (pembro) in microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) advanced solid tumors. *J Clin Oncol*. 2025;43(16_suppl):4019–4019.

About the Authors



Arwa Ahmed Abdelrahim, MD

Dr. Arwa Ahmed Abdelrahim presently is a medical oncology fellow specializing in GI oncology at The Ottawa Hospital Cancer Center. She earned her MBBS and MD degrees from the University of Bahri in Sudan, and later specialized in internal medicine and medical oncology at Hamad Medical Corporation in Qatar. During her medical oncology fellowship in Qatar, she contributed to the reorganization of the Hepato-pancreatobiliary Tumor Board (HPB MDT). Dr. Ahmed interests comprise clinical research in GI oncology and translational research.

Affiliations: Division of Medical Oncology, Department of Medicine, University of Ottawa, Ottawa, ON



Rachel Goodwin, MD

Dr. Goodwin is currently Associate Professor at the University of Ottawa, The Ottawa Hospital Cancer Centre. Dr. Goodwin completed her medical school and medical oncology training at University of Ottawa, The Ottawa Hospital. She went on to complete a two-year Drug Development Fellowship at CCTG (Canadian Cancer Trials Group), Queen's University, Kingston. She has now worked in Ottawa for close to fifteen years in the areas of gastrointestinal malignancies. She is actively involved in clinical trials via her role as CCTG Colon Disease Site Co-chair and Chair of GI Clinical trials at The Ottawa Hospital Cancer Centre. She has a keen interest in transitioning biomarker-based systemic therapy into clinical practice. Dr. Goodwin is the Medical Oncology co-chair for the Gastrointestinal Disease Site Group, Program in Evidence Based Care for Ontario.

Affiliations: Division of Medical Oncology, Department of Medicine, University of Ottawa The Ottawa Hospital Research Institute, Ottawa, ON.

First-line Treatment Selection for Advanced Unresectable Biliary Tract Cancer

Arwa Ahmed Abdelrahim, MD
Rachel Goodwin, MD

Introduction

Biliary tract cancer (BTC) comprises a group of heterogeneous malignancies that arise from the bile ducts (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma) and the gallbladder (gallbladder cancer). Collectively, these malignancies carry a poor prognosis, which is attributed to the advanced stage at presentation. Historically, advanced BTC had a reputation of being less responsive to chemotherapy, a theory that was changed in the last decade, likely due to improved biliary drainage techniques that consequently improve liver function. Few advances have been made in the treatment of advanced and unresectable BTC in the past couple of years.

Overview of First-line Treatment

Chemotherapy

Before 2010, no standard chemotherapy regimen was available for treating advanced BTC. Patients were usually treated with chemotherapy used for pancreatic adenocarcinoma, such as gemcitabine or fluoropyrimidine as single agents or in combination with other drugs. Different chemotherapy combination regimens were primarily investigated in Phase II trials.

The Advanced Biliary Cancer (ABC-02) randomized phase III trial proved superiority of the combination gemcitabine and cisplatin over gemcitabine alone, resulting in a median overall survival (mOS) of 11.7 months (95% confidence interval [CI]: 9.5–14.3) compared to 8.1 months (95% CI: 7.1–8.7) and median progression-free survival (mPFS) of 8 months (95% CI: 6.6–8.6) compared to 5 months (95% CI: 6.6–8.6) favouring the combination.¹ The ABC-02 trial was an extension of this prior ABC-01 trial, and also

showed an improved tumour control rate with the same combination regimen compared to gemcitabine alone.²

The adverse events reported in the ABC-02 trial were comparable between the two treatment groups, except for liver function, which was worse in the gemcitabine alone group (27.1%) than in the combination group (16.7%). This might be explained by improved disease control in the combination group, allowing better biliary drainage. In the real-world clinic, the combination regimen seems generally well tolerated by patients.

Other chemotherapy doublets (e.g., capecitabine + cisplatin, gemcitabine + oxaliplatin) failed to improve outcomes compared to gemcitabine plus cisplatin.^{3,4} While triplet chemotherapy regimens (e.g., mFOLFIRINOX [oxaliplatin + leucovorin + irinotecan + fluorouracil], gemcitabine + albumin-bound paclitaxel + gemcitabine, GEMOX [gemcitabine + oxaliplatin] + capecitabine) showed better response rates compared to gemcitabine plus cisplatin, it did not translate into statistically significant improvement in OS.⁵⁻⁷ Gemcitabine and cisplatin remained the standard of care for over a decade until the practice-changing TOPAZ-1 trial.

Combination Chemotherapy with an Immune Checkpoint Inhibitor (ICI)

TOPAZ-1 was a double-blind, placebo-controlled randomized Phase III trial investigating the addition of durvalumab to the gemcitabine and cisplatin combination.⁸ A total of 685 patients who had previously untreated or recurrent metastatic or unresectable advanced BTC were randomly assigned to receive either durvalumab or placebo with gemcitabine and cisplatin for eight cycles, followed by maintenance durvalumab or placebo. The study showed an improvement in median OS with the durvalumab

chemotherapy combination having an OS of 12.8 months (95% CI: 11.1–14.0) compared to 11.5 months (95% CI: 10.1–12.5) for the chemotherapy plus placebo group (hazard ratio [HR]: 0.80; 95% CI: 0.66–0.97; $P=0.021$). The PFS also improved with a median PFS of 7.2 months (95% CI: 6.7–7.4) for the durvalumab combination group, compared to 5.7 months (95% CI: 5.6–6.7) for the placebo group.

The outcomes in this study were observed to be better and more pronounced with treatment beyond six months. The estimated OS rate at 24 months was 24.9% (95% CI: 17.9–32.5) for the durvalumab group compared to 10.4% (95% CI: 4.7–18.8) for the placebo group. No increased toxicity was reported using the durvalumab plus chemotherapy combination, with comparable rates of Grade 3 or 4 adverse events in both groups (75.7% vs. 77.8% for the durvalumab and the placebo group, respectively). The addition of immunotherapy was tolerable, with Grade 3/4 immune-related adverse events reported as 2.4% in the chemotherapy plus durvalumab arm.

The Phase III KEYNOTE-966 trial had a similar design but enrolled more patients ($N=1069$).⁹ Patients with unresectable locally advanced or metastatic BTC were randomized to receive either pembrolizumab or placebo in combination with gemcitabine and cisplatin for 8 cycles, followed by maintenance gemcitabine combined with pembrolizumab or placebo. The median OS was longer in the pembrolizumab group, at 12.7 months (95% CI: 11.5–13.6) compared to 10.9 months (95% CI: 9.9–11.6) in the placebo group (HR: 0.83 [95% CI: 0.72–0.95]) with estimated OS rates at 24 months of 25% (95% CI: 21–29) and 18% (95% CI: 15–22) for the pembrolizumab and the placebo group, respectively. The median PFS in the pembrolizumab group was 6.5 months (95% CI: 5.7–6.9) compared to 5.6 months (95% CI: 5.1–6.6) in the placebo group.

Therefore, the TOPAZ-1 and KEYNOTE-966 studies showed improved outcomes using a combination of an ICI with the standard of care chemotherapy, making their way to become the first-line treatment choice in advanced or metastatic BTC. These combination regimens had an acceptable safety profile, with comparable results in Grade 3 or 4 adverse events in TOPAZ-1 and KEYNOTE-966 (75.7% vs. 77.8%) and (79% vs. 75%), respectively.

Targeted Therapy

Next-generation sequencing (NGS) has improved our understanding of the BTC molecular profile. Various mutations, amplifications, and gene alterations have been described in BTC, with varying incidence in each tumour subtype reflecting their different etiology (**Figure 1**). The therapeutic implications of some of these alterations were established using targeted therapy in different studies over the last decade.

The incidence of high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) in BTC is low, ranging between 1% and 3%, and can be either hereditary, as in Lynch Syndrome-associated tumours, or sporadic.^{10,11} Testing for MSI-H/dMMR has gained interest for almost all solid tumours as a useful predictor of response to ICI.¹² In the Phase II trial KEYNOTE-158, the use of pembrolizumab in patients with MSI-H/dMMR solid tumours (non-colorectal) resulted in a clinically meaningful mOS of 20.1 months (95% CI: 14.1–27.1).¹³ The objective response rate (ORR) was 30.8% (95% CI: 25.8%–36.2%) with a median duration of response of 47.5 months. This study enrolled 351 patients, of whom 22 (6.3%) had BTC.

Dostarlimab is another ICI monoclonal antibody that inhibits the programmed cell death 1 receptor (PD-1) and has shown proven clinical activity in MSI-H/dMMR solid tumours. In the Phase I multicenter GARNET trial with 327 patients enrolled, of which 10 patients (3.1%) had BTC, dostarlimab had an ORR of 44.0% (95% CI: 38.6%–49.6%), with 72.2% of the responders having a lasting response for 12 months or longer.¹⁴

With the approval of gemcitabine and cisplatin plus ICI in advanced or unresectable BTC, ICI is available for rare cases of MSI-H/dMMR BTC. ICI is considered standard practice in these patients, provided there is no contraindication to immunotherapy. No studies have compared chemotherapy plus ICI versus ICI alone in this patient population. However, in clinical scenarios where chemotherapy toxicity occurs, we recommend discontinuing chemotherapy and continuing ICI monotherapy.

Human epidermal growth factor receptor 2 (HER2), is a membrane tyrosine kinase receptor protein that is known to promote cell growth and proliferation in various cancer types when overexpressed or amplified. In BTC HER 2 is more prevalent in Gallbladder Cancer with reported incidence 15–30%, compared to 10–20% in

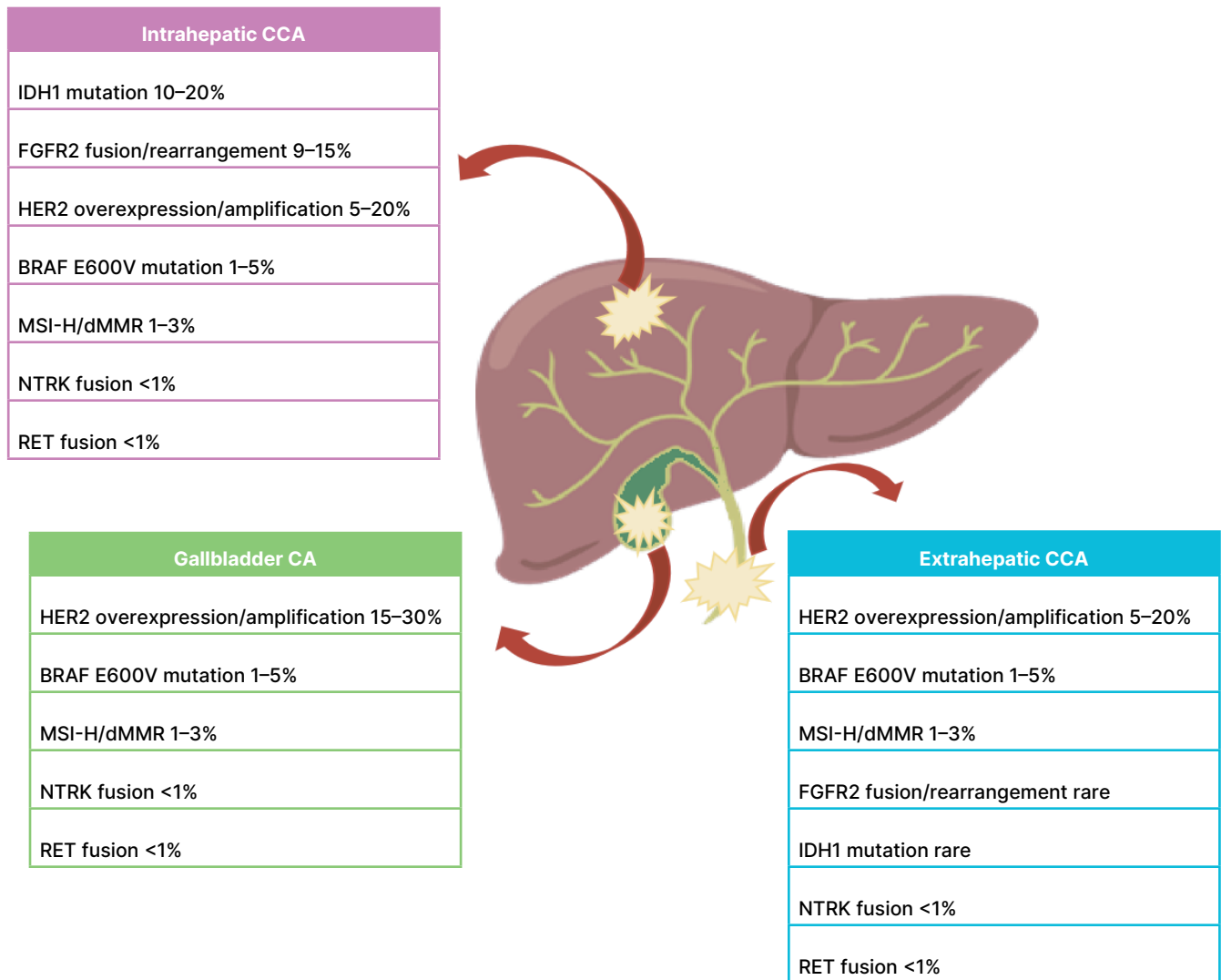


Figure 1. Mutations, amplifications, and gene alterations in biliary tract cancer. Varying incidence in each tumour subtype reflects their different etiology; courtesy of Arwa Ahmed Abdelrahim, MD, and Rachel Goodwin, MD.

Abbreviations: **CA:** carcinoma; **CCA:** choriocarcinoma; **dMMR:** deficient in mismatch repair; **FGFR:** fibroblast growth factor receptor; **HER2:** receptor tyrosine-protein kinase erbB-2; **IDH:** isocitrate dehydrogenase; **MSI-H:** high microsatellite instability; **NTRK:** neurotrophic tyrosine kinase receptors.

extrahepatic cholangiocarcinoma (ECC) and 3–5% in intrahepatic cholangiocarcinoma (ICC).¹⁵ Over the years, there is cumulative evidence showing clinical activity of targeting HER2 in BTC with different agents mostly after progressing on one or more lines of therapy. Zanidatamab is a bispecific humanized monoclonal antibody that inhibits the HER2 protein via two different domains with proven clinical activity in BTC after progressing on Gemcitabine based chemotherapy.¹⁶ HERIZON BTC-302 is an ongoing

randomized phase 3 clinical trial investigating the addition of Zanidatamab to the first line standard of care therapy Gemcitabine and Cisplatin with or without ICI in HER2 positive advanced BTC.¹⁷ The trial is looking at efficacy and safety of Zanidatamab in the first line treatment setting with PFS as the primary end point in HER2 positive IHC +3 patients. This is the first phase 3 clinical trial addressing integrating molecular alterations in the first line therapy in BTC and the results may shape the treatment for this subset of patients.

Treatment Selection

First-line Treatment

The selection of first-line treatment in advanced or metastatic BTC tumours with proficient or unknown MMR status depends on many factors, such as the drug availability/coverage, patient's performance status, concurrent medical conditions (e.g., contraindication to immunotherapy), and past medical history. In Canada, for patients with advanced BTC without contraindications to ICI, gemcitabine and cisplatin plus ICI is the standard of care for first-line treatment. A Health Canada indication for chemotherapy plus durvalumab was announced in 2022, followed by chemotherapy plus pembrolizumab in 2023. Clinical guidelines quote the use of either durvalumab or pembrolizumab in combination with chemotherapy as an acceptable option.¹⁸ Both drugs are given with the same chemotherapy regimen for 8 cycles followed by maintenance either alone (durvalumab) or combined with gemcitabine (pembrolizumab). The decision to continue maintenance gemcitabine + ICI depends on many factors, including the patient's chemotherapy side effects, such as myelosuppression, performance status, and ability to tolerate two systemic therapy drugs, and willingness to come to the cancer centre every 3 weeks versus every 4 weeks for infusions. A pro-con discussion can aid in this decision.

The chemotherapy combination of gemcitabine and cisplatin without ICI remains a first-line option for advanced BTC. In the TOPAZ-1 trial, 18% of patients reported a partial response on the placebo arm and 0.6% had a complete response. Chemotherapy alone is an appropriate choice for patients who have a contraindication to ICI, for example, in patients with an organ transplant, moderate to severe autoimmune disease, or previous severe ICI-related toxicity. Carboplatin can be used as a substitute for cisplatin if toxicity requires. Single-agent gemcitabine is recommended for patients who are not candidates for doublet chemotherapy regimens due to poor performance status.

Later Lines of Treatment

After the first-line treatment, patients with progressive BTC have poor survival outcomes, and the chance to receive second-line therapy is limited to patients with a good performance status. No standard second-line treatment exists for advanced or metastatic BTC; however, fluorouracil-based chemotherapy is usually used in this scenario after progression on a gemcitabine combination.

FOLFOX chemotherapy became a widely accepted treatment option after the Phase III ABC-06 trial that showed improvement in OS when adding second-line FOLFOX to active symptom control compared to only active symptom control, resulting in an OS of 6.2 months vs. 5.3 months, with a 12-month OS rate of 25.9% vs. 11.4%, respectively.¹⁹ Other treatment regimens can also be used, including FOLFIRI (leucovorin, fluorouracil, irinotecan) and the tyrosine kinase inhibitor regorafenib.^{20,21}

Targeted therapy can be more effective compared to chemotherapy. Many studies have shown clinical anti-tumour activity of drugs targeting molecular alterations in advanced BTC in the second-line and beyond. Identifying the tumour molecular profile using genomic sequencing or NGS is best performed early upon presentation with advanced disease. Availability and funding for the tests and drugs are the main obstacles that steer the treatment selection process away from or toward a specific therapy. We have summarized the targetable molecular alterations in BTC and the relevant studies with targeted therapies in **Table 1**.

Future Directions

The most significant advancement in the first-line BTC treatment has been the addition of ICI to the standard chemotherapy regimen of gemcitabine and cisplatin. However, biomarkers that predict which patients will gain the greatest benefit from immunotherapy remain lacking.

BTC are still treated collectively as one disease, although the advances in genomic studies have shown that they may not only have a different anatomical location, but they may also exhibit different genetic alterations governing the pathogenesis of each disease subtype. This highlights the importance of studies focusing on moving targeted therapies to the first-line setting.

Biomarker	Drug	Trial	Phase	Tumour type	Line	N	Primary endpoint
IDH1 mutation	Ivosidenib	ClarIDHy ^{22,23}	III	CCA	2 nd or 3 rd	185	mPFS: 2–7 months
FGFR2 rearrangement/fusion	Pemigatinib	FIGHT-202 ²⁴	II	CCA	2 nd or more	107	ORR: 35.5%
	Futibatinib	FOENIX-CCA2 ²⁵	II	iCCA	2 nd or more	103	ORR: 42%
HER2neu overexpression/ amplification	Pertuzumab + trastuzumab	MyPathway ²⁶	IIa	BTC	2 nd or more	39	ORR: 23%
	Zanidatamab	HERIZON-BTC-01 ¹⁶	IIb	BTC	2 nd	80	ORR: 41.3%
	Tucatinib + trastuzumab	SGNTUC-019 ²⁷	II	BTC cohort	2 nd or more	30	ORR: 46.7%
	Trastuzumab deruxtecan	HERB ²⁸	II	BTC	2 nd	22	ORR: 36.4%
NTRK fusion	Entrectinib	STARTRK-2 ²⁹	II	Basket trial	Any line	155	ORR: 61.3%
	Larotrectinib	NAVIGATE ³⁰	I/II	Basket trial	Any line	55	ORR: 75%
RET fusion	Pralsetinib	ARROW ³¹	I/II	Basket trial	Any line	29	ORR: 57%
BRAF V600E	Dabrafenib + trametinib	ROAR ³²	II	BTC cohort	2 nd or more	43	ORR: 47%

Table 1. Targetable molecular alterations in biliary tract cancer and pivotal studies; *courtesy of Arwa Ahmed Abdelrahim, MD, and Rachel Goodwin, MD.*

Abbreviations: **FGFR:** fibroblast growth factor receptor; **HER2:** receptor tyrosine-protein kinase erbB-2; **IDH:** isocitrate dehydrogenase; **mPFS:** median progression-free survival; **NTRK:** neurotrophic tyrosine kinase receptor; **ORR:** objective response rate.

Circulating tumour DNA (ctDNA) assessment is an emerging technique that is now widely used for different solid tumour studies and has the potential to overcome tumour heterogeneity. In BTC, ctDNA can be used to identify arising oncogenic drivers responsible for the acquired resistance to chemotherapy or targeted therapy or can be used to identify genetic alterations to help inform treatment selection. In a comprehensive study that looked at cell-free DNA (cfDNA), which combines ctDNA and circulating tumour cells (CTC), in samples from 1,671 patients with advanced BTC, actionable genetic alterations were detected in 44% of patients.³³ This analysis reported the concordance between cfDNA and tissue for detecting mutations was high for *IDH1* mutations (87%) and the *BRAF* V600E mutation (100%), while it was low for detecting *FGFR2* fusions (18%). These correlation studies are critical given that obtaining adequate tissue from locally advanced, non-surgical patients is often challenging.

Conclusion

Advancing the treatment of BTC remains an unmet need among solid tumours. With the addition of ICI to chemotherapy in recent years, meaningful improvement has been observed in the treatment of advanced BTC, putting durvalumab and pembrolizumab as equally effective additions to chemotherapy.

The advances in molecular profile assessment not only improved our understanding of the different disease subtypes but also paved the way to explore targeted therapies, adding more treatment options after progression on first-line treatment. The treatment selection is more challenging beyond the first-line, and is dictated by actionable genomic alterations, performance status, patient's preferences, availability, and cost.

Recognizing the importance of molecular testing, Canadian Cholangiocarcinoma Collaborative (C3) has supported a Canadian testing program to improve accessibility of patients to these tests. In addition, C3 has expert tumour board meetings with the goal of discussing treatment selection, educating on identified molecular alterations, and reviewing access to clinical trials.

Correspondence

Rachel Goodwin, MD

Email: rgoodwin@toh.ca

Financial Disclosures

A.A.: None declared.

R.G.: Honoraria for speaker board/advisory board:

AAA, Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, CPD Network, Eisai, Ipsen, Merck, Pfizer;

Independent educational grant: Apobiologix, Ipsen, Pfizer; **Travel grant:** Ipsen

References

1. Valle J, Wasan H, Palmer DH. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-81. doi: 10.1056/NEJMoa0908721.
2. Valle JW, Wasan H, Johnson P. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - The UK ABC-01 Study. *Br J Cancer*. 2009;101(4):621-7. doi: 10.1038/sj.bjc.6605211.
3. Sharma A, Kalyan Mohanti B, Pal Chaudhary S, Sreenivas V, Kumar Sahoo R, Kumar Shukla N, et al. Modified gemcitabine and oxaliplatin or gemcitabine + cisplatin in unresectable gallbladder cancer: Results of a phase III randomised controlled trial. *Eur J Cancer*. 2019;123:162-170. doi: 10.1016/j.ejca.2019.10.004.
4. Lee J, Hong TH, Lee IS, You YK, Lee MA. Comparison of the efficacy between gemcitabine-cisplatin and capecitabine-cisplatin combination chemotherapy for advanced biliary tract cancer. *Cancer Res. Treat*. 2014;47:259-265. doi: 10.4143/crt.2013.230.
5. Phelip JM, Desrame J, Edeline J, Barbier E, Terrebbonne E, Michel P, et al. Modified FOLFIRINOX Versus CISGEM chemotherapy for patients with advanced biliary tract cancer (PRODIGE 38 AMEBICA): A randomized phase II study. *J Clin Oncol*. 2022;40:262-271. doi: 10.1200/JCO.21.00679.
6. Shroff RT, Guthrie KA, Scott AJ, Borad MJ, Goff LW, et al. SWOG 1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. *J Clin Oncol*. 2023;41:LBA490.

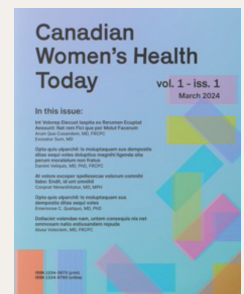
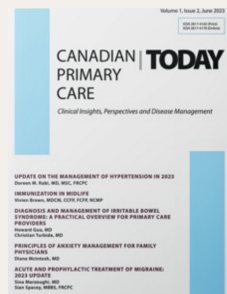
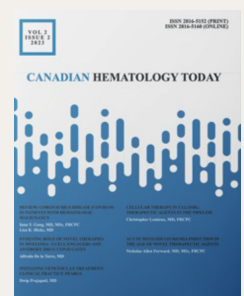
7. Markussen A, Jensen LH, Diness LV, Larsen FO. Treatment of patients with advanced biliary tract cancer with either oxaliplatin, gemcitabine, and capecitabine or cisplatin and gemcitabine—A randomized phase II trial. *Cancers*. 2020;12:1975. doi: 10.3390/cancers12071975.
8. Oh DY, Ruth He A, Qin S, Chen LT, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evid*. 2022;1(8):EVIDoa2200015. doi: 10.1056/EVIDoa2200015.
9. Kelley RK, Ueno M, Yoo C. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10391):1853-1865. doi: 10.1016/S0140-6736(23)00727-4.
10. Vanderwalde A, Spetzler D, Xiao N. Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. *Cancer Med*. 2018;7(3):746-756. doi: 10.1002/cam4.1372.
11. Hause RJ, Pritchard CC, Shendure J. Classification and characterization of microsatellite instability across 18 cancer types. *Nat Med*. 2016;22(11):1342-1350. doi: 10.1038/nm.4191.
12. Le DT, Durham JN, Smith KN. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409-413. doi: 10.1126/science.aan6733.
13. Maio M, Ascierto PA, Manzyuk L. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. *Ann Oncol*. 2022;33(9):929-938. doi: 10.1016/j.annonc.2022.05.519.
14. André T, Berton D, Curigliano G. Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient solid tumors: A nonrandomized controlled trial. *JAMA Netw Open*. 2023;6(11):e2341165. doi: 10.1001/jamanetworkopen.2023.41165.
15. Juan W Valle, Angela Lamarca, Lipika Goyal. New Horizons for Precision Medicine in Biliary Tract Cancers. *Cancer Discov*. 2017 Sep;7(9):943-962. doi: 10.1158/2159-8290.CD-17-0245. Epub 2017 Aug 17.
16. Harding JJ, Fan J, Oh DY. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *Lancet Oncol* 2023;24:772-782.
17. James J. Harding, Teresa Macarulla, Shubham Pant. HERIZON-BTC-302: A phase 3 study of zanidatamab with standard-of-care (SOC) therapy vs SOC alone for first-line treatment of human epidermal growth factor receptor 2 (HER2)-positive advanced/metastatic biliary tract cancer (BTC). *Journal of Clinical Oncology*. https://doi.org/10.1200/JCO.2025.43.4_suppl.TPS64
18. Leigh J, Ahmed A, Aubin F. Eastern Canadian Gastrointestinal Cancer Consensus Conference 2024. *Curr Oncol*. 2025;32(3):175. doi: 10.3390/currenol32030175.
19. Angela Lamarca, Daniel H Palmer, Harpreet Singh Wasan. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol*. 2021 May;22(5):690-701. doi: 10.1016/S1470-2045(21)00027-9. Epub 2021 Mar 30.
20. Caparica R, Lengele A, Bekolo W, Hendlisz A. FOLFIRI as second-line treatment of metastatic biliary tract cancer patients. *Autops Case Rep* 2019;9:e2019087.
21. Sun W, Patel A, Normolle D. A phase 2 trial of regorafenib as a single agent in patients with chemotherapy-refractory, advanced, and metastatic biliary tract adenocarcinoma. 2019;125(6):902-909. doi: 10.1002/cncr.31872.
22. Abou-Alfa GK, Macarulla T, Javle MM. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(6):796-807. doi: 10.1016/S1470-2045(20)30157-1.
23. Zhu AX, Macarulla T, Javle MM. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: The Phase 3 randomized clinical ClarIDHy trial. *JAMA Oncol*. 2021;7(11):1669-1677. doi: 10.1001/jamaoncol.2021.3836.
24. Ghassan K Abou-Alfa, Vaibhav Sahai, Antoine Hollebecque. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020 May;21(5):671-684. doi: 10.1016/S1470-2045(20)30109-1. Change the number according to order
25. Goyal L, Meric-Bernstam F, Hollebecque A. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388(3):228-239. doi: 10.1056/NEJMoa2206834.

26. Javle M, Borad MJ, Azad NS. Pertuzumab and trastuzumab for HER2-positive metastatic biliary tract cancer (MyPathway): A multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2021;22:1290-1300.
27. Nakamura Y, Mizuno N, Sunakawa Y. Tucatinib and trastuzumab for previously treated human epidermal growth factor receptor 2-positive metastatic biliary tract cancer (SGNTUC-019): A phase II basket study. *J Clin Oncol* 2023;41:5569-5578.
28. Ohba A, Morizane C, Kawamoto Y. Trastuzumab deruxtecan in human epidermal growth factor receptor 2-expressing biliary tract cancer (HERB; NCCCH1805): A multicenter, single-arm, phase II trial. *J Clin Oncol*. 2024;42(27):3207-3217. doi: 10.1200/JCO.23.02010.
29. Krzakowski MJ, Lu S, Cousin S. Updated analysis of the efficacy and safety of entrectinib in patients (pts) with locally advanced/metastatic NTRK fusion-positive (NTRK-fp) solid tumors [ASCO abstract] *J Clin Oncol*. 2022;40(16_suppl):3099. doi: 10.1200/JCO.2022.40.16_suppl.3099.
30. Drilon A, Laetsch TW, Kummar S. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018;378:731-739.
31. Subbiah V, Cassier PA, Siena S. Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med* 2022;28:1640-1645.
32. Subbiah V, Lassen U, Élez E. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 2020;21:1234-1243.
33. Berchuck JE, Facchinetti F, DiToro DF. The clinical landscape of cell-free DNA alterations in 1671 patients with advanced biliary tract cancer. *Ann Oncol* 2022;33:1269-83.



Medical minds gather here.

As the largest independent medical publisher in Canada, our peer-reviewed open access scientific journals are a practical resource for Canadian healthcare practitioners. We currently publish specialty journals in the areas of allergy & immunology, dermatology, hematology, ophthalmology, diabetes & endocrinology, gastroenterology, primary care, women's health, rheumatology, oncology, respirology and our press is constantly growing with new titles planned.



Original Research: Biomarker Testing in a Canadian Centre for Patients with Non-small Cell Lung Cancer: **Assessing Residual Risks**

Yunting Liu^{1,2}, Steven Shen³, Manav Shukla³, Janet Malowany^{3,4}, Shaheed Hakim^{3,4}, Zared Aziz^{3,4}, David N. Parente⁶, Victoria Cheung⁶, Suneil Khanna⁵, Yoo-Joung Ko⁵, Wondwossen Kidanewold^{3,4}, Michael A. Ko⁶, Kelsie L. Thu^{3,7}, and Ju-Yoon Yoon^{8,9}

Affiliations: 1. Department of Physiology, University of Toronto, Toronto, ON
 2. Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, ON
 3. Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
 4. Department of Laboratory Medicine, Unity Health Toronto, Toronto, Ontario, Canada
 5. Division of Medical Oncology, Unity Health Toronto, Toronto, Ontario, Canada
 6. Division of Thoracic Surgery, Unity Health Toronto, Toronto, Ontario, Canada
 7. Keenan Research Centre for Biomedical Science, Unity Health Toronto, Toronto, Ontario, Canada
 8. Department of Pathology, Shared Health Manitoba, Winnipeg, MB
 9. Department of Pathology, University of Manitoba, Winnipeg, MB

Biomarker testing is critical for guiding treatment decisions and clinical management in patients with non-small cell lung cancer (NSCLC). Although the clinical utility of comprehensive testing for point mutations and gene rearrangements is well established, access to next-generation sequencing (NGS)-based assays in Ontario has historically been limited due to provincial funding constraints.

We conducted a retrospective chart review of 215 patients diagnosed with lung adenocarcinoma over a five-year period (2016-2021) and report the observed biomarker testing practice. Testing primarily comprised polymerase chain reaction (PCR)-based detection of common epidermal growth factor receptor (EGFR) mutations and immunohistochemistry (IHC) for anaplastic lymphoma kinase (ALK) overexpression, with or without confirmatory fluorescence in situ hybridization (FISH), and programmed death-ligand 1 (PD-L1) IHC. IHC for ROS1 overexpression, as a surrogate for ROS1 fusion, was observed in the first quarter of 2020. Routine panel-based NGS testing was implemented in the first quarter of 2021. Noting the differences between PCR- and NGS-based EGFR assessment, risks of “false negative” were estimated based on Bayesian analyses. Given the limited scope of PCR tests in terms of variants detected, the post-test, residual risk of “false negative” EGFR was estimated to range ~1:90 in white, Caucasian patients, to ~1:9 in Asian patients.

We observed consistent implementation of EGFR, ALK, and PD-L1 testing during the study period, which was in alignment with 2017 National Comprehensive Cancer Network (NCCN) guideline recommendations. However, the delayed adoption of ROS1 testing and NGS-based profiling, including assays for MET and RET alterations, reflects broader limitations in provincial funding policy and highlights the need for equitable access to comprehensive biomarker testing in Ontario.

Introduction

Clinical management of non-small cell lung cancer (NSCLC) is increasingly guided by biomarker testing, which has become a cornerstone of precision oncology and is now embedded in standard clinical care. The use of broad next-generation sequencing (NGS) panels is routinely recommended for patients with NSCLC to identify oncogenic drivers—including point mutations and gene rearrangements—as reflected in the most recent National Comprehensive Cancer Network (NCCN) guidelines.^{1,2} However, the high cost of NGS has been a limiting factor in many jurisdictions, including Canada. In Ontario, the introduction of a “comprehensive” cancer biomarker testing program aimed to expand access to molecular testing for NSCLC, incorporating both NGS and programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) assessments. In 2021, Ontario Health–Cancer Care Ontario (OH-CCO) endorsed NGS as the preferred initial test at diagnosis, replacing single-gene assays. This policy shift followed a period in which alternative molecular testing approaches were more commonly used in lieu of NGS.

The value of biomarker testing in informing prognosis and guiding targeted therapies is well established. NGS offers the advantage of simultaneously detecting a broad range of actionable alterations, including *MET* exon 14 skipping mutations and *RET* gene rearrangements, providing a more comprehensive molecular profile of each patient’s tumour. With consistent provincial funding, patients diagnosed with NSCLC in Ontario are more likely to receive equitable access to molecular diagnostics, enabling clinicians to integrate precision oncology into treatment planning. Robust biomarker testing may be especially important in a diverse metropolitan area such as Toronto, where a large proportion of patients identify as immigrants from East or South Asia, or as members of Indigenous communities. While *EGFR* mutations are known to be more prevalent in certain Asian populations³, the distribution of targetable oncogenic drivers in North American multi-ethnic cohorts remains incompletely understood.

In this study, we examined biomarker testing practices among patients with NSCLC diagnosed at a single academic centre in Toronto between 2016 and 2021. We describe the transition from predominantly non-NGS testing to implementation of panel-based NGS and assess the potential

clinical impact of limited variant detection, including the risk of false-negative results in certain patient subgroups.

Materials & Methods

Study Design and Cohort Selection

This was a single-centre, retrospective cohort study conducted at Unity Health Toronto, an academic tertiary care hospital in Ontario, Canada. A total of 265 consecutive patients diagnosed with NSCLC between 2016 and 2021 were identified through electronic medical records (EMRs) and included for demographic and clinical characterization. Patients diagnosed with neuroendocrine neoplasms (including typical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma) or pleomorphic carcinoma were excluded. To analyze biomarker testing patterns, we focused on 215 patients with histologically confirmed adenocarcinoma or adenosquamous carcinoma, as these histologic subtypes are routinely considered for molecular profiling per clinical guidelines. Patients with squamous cell carcinoma ($n = 50$) were excluded from biomarker testing analysis due to the low prevalence of actionable driver mutations in this subgroup.

Biomarker Testing Methodology

All biomarker testing was performed as send-out assays to external reference laboratories. For *EGFR* testing, PCR-based assays targeting the most common sensitizing mutations (exon 19 deletions and exon 21 p.L858R substitutions) were utilized. *ALK* gene rearrangements were assessed by IHC, typically using the D5F3 clone, with fluorescence *in situ* hybridization (FISH) performed at the discretion of the testing laboratory. PD-L1 testing was generally conducted using either the SP263 or 22C3 clone, depending on institutional protocol and availability. *ROS1* testing by IHC (clone D4D6) was introduced in the first quarter (Q1) of 2020.

NGS was implemented in Q1 2021 using a hybrid capture-based panel covering hotspot mutations, gene rearrangements, and copy number alterations. Prior to that, single-gene testing approaches predominated. Biomarker testing decisions were made at the discretion of treating oncologists or pathologists, generally based on tumour histology, disease stage, and sample availability.

Demographic Classification

Race and ethnicity were not discretely captured in the EMRs. To approximate *EGFR* mutation prevalence by race, patients were classified as “Asian” or “Non-Asian” using surname inference, supplemented by preferred language and country of birth, where available. The “Asian” category included East, Southeast, and South Asian patients; “Non-Asian” patients were presumed to be predominantly white/Caucasian. This classification was used for subgroup-based modelling of false-negative risk associated with PCR-based *EGFR* testing.

Statistical Analysis

Descriptive statistics were used to summarize cohort characteristics and biomarker testing frequencies. Differences between observed and expected mutation frequencies were assessed using two-tailed Chi-square tests, with a *p*-value <0.05 considered statistically significant.

Bayesian modelling was applied to estimate the risk of false-negative results associated with PCR-based *EGFR* testing. Published prevalence estimates for *EGFR* mutations in Asian and white populations were used to establish pre-test probabilities. Assuming 90% sensitivity and ~100% specificity for PCR assays, post-test probabilities were calculated using Bayes’ theorem. This model allowed estimation of the residual risk of undetected *EGFR* mutations following a negative PCR result, stratified by racial background. All statistical analyses were conducted in R (base version 4.1.1).

Results

Biomarker Testing Patterns in NSCLC Cohort

The mean age at diagnosis was 68 years. The slight majority of patients (137/265, 51.7%) were male. Where cigarette smoking status was available, 144 of 203 patients (70.9%) reported a history of tobacco use. Adenocarcinoma was the most common histologic diagnosis, identified in 211 of 265 patients (79.6%), followed by 50 patients with squamous cell carcinoma, and 4 patients with adenosquamous carcinoma. Most patients (63.9%) were diagnosed at American Joint Committee on Cancer (AJCC) Stage I (8th edition). One patient was diagnosed at Stage 0, 167 at Stage I, 31 at Stage II, 41 at Stage III, and 23 at Stage IV. Staging

data were unavailable for two patients. The median follow-up period was two years.

All biomarker studies during the study period were performed as send-out assays to external reference laboratories. For patients with adenocarcinoma or adenosquamous carcinoma (*n*=215), biomarker testing primarily consisted of: polymerase chain reaction (PCR)-based detection of common epidermal growth factor receptor (*EGFR*) mutations, such as exon 19 deletions and exon 21 p.L858R; immunohistochemistry (IHC) for overexpression of anaplastic lymphoma kinase (*ALK*), used as a surrogate for *ALK* gene rearrangement and performed with or without fluorescence *in situ* hybridization (FISH); and IHC for programmed death-ligand 1 (PD-L1) expression (Figure 1). *ROS1* IHC, used as a surrogate marker for *ROS1* gene rearrangement, was implemented in Q1, 2020. Routine panel-based next-generation sequencing (NGS) testing was adopted in Q1, 2021. In comparison, the 2017 National Comprehensive Cancer Network (NCCN) guidelines had already incorporated *ROS1* testing into the main diagnostic algorithm, and included the option of either PCR-based or NGS-based testing for *EGFR* mutations.²

Impact Assessment

In constitutional genetics, Bayesian analysis has been employed to calculate pre- and post-test probabilities for pathogenic germline variants. For example, cystic fibrosis risk associated with cystic fibrosis transmembrane conductance regulator (*CFTR*) gene variants differs across ethnic groups, as certain mutations are more prevalent in specific populations; accordingly, assay design can substantially influence the residual risk following a negative test result.^{4,5} Although this framework is not routinely applied in cancer genetics, it can offer useful insights into differences in test performance across populations.⁶ In this study, we applied Bayesian analysis to estimate the potential impact of relying on non-NGS methods for NSCLC biomarker testing.

EGFR mutations have been reported in approximately 10% of white, Caucasian patients with NSCLC, up to 19% of Black patients, and as high as 50% of Asian patients.^{3,7,8} Exon 19 deletions and exon 21 p.L858R variants comprise approximately 85–90% of the *EGFR* alterations.⁹ Given that many PCR-based platforms are limited to detecting only these common variants, it can be inferred that 10–15% of *EGFR* mutations would have been missed. Assuming a sensitivity of 90%

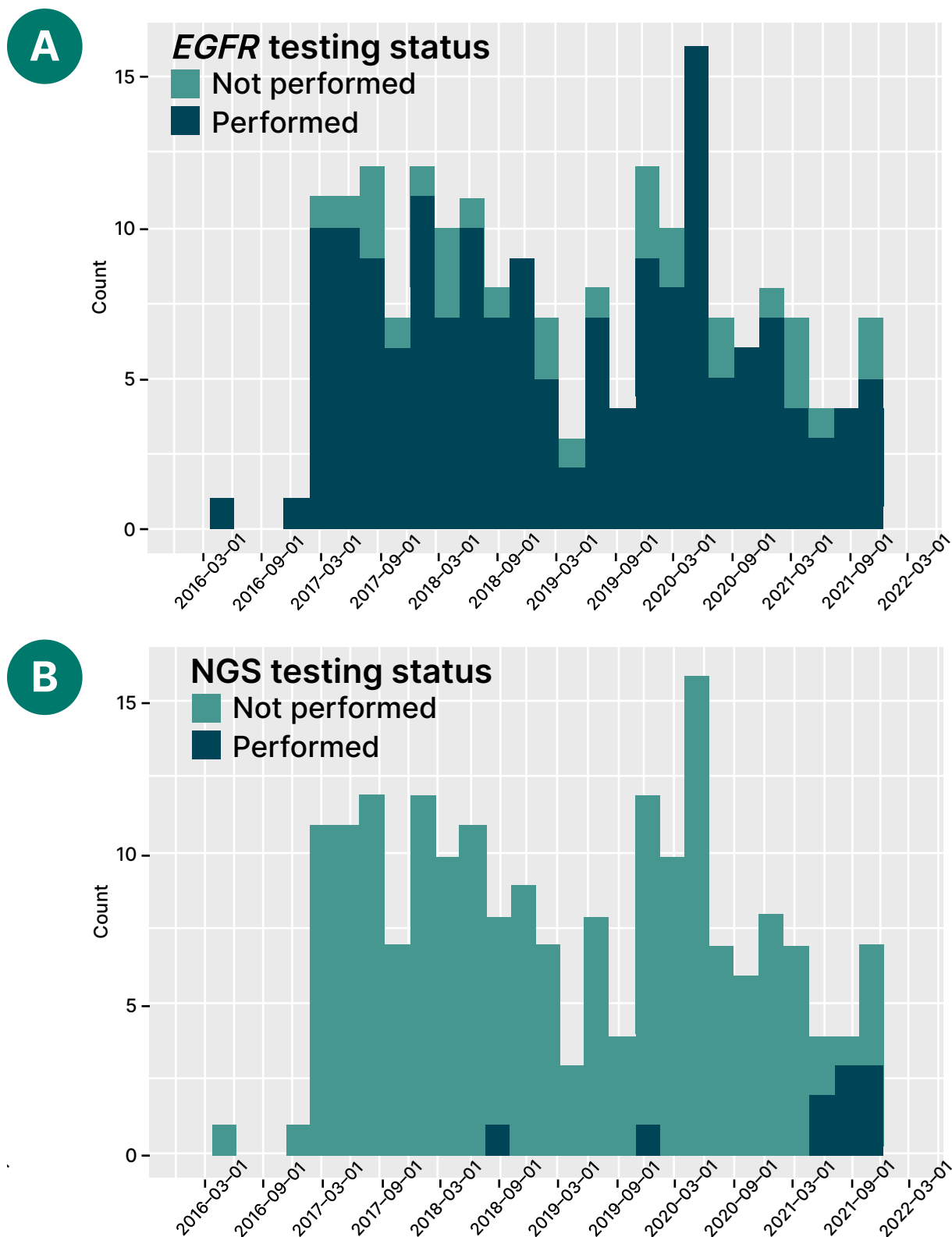


Figure 1. A) EGFR and B) next-generation sequencing (NGS) testing patterns during our study period; courtesy of Yunting Liu, Steven Shen, Manav Shukla, Janet Malowany, Shaheed Hakim, Zared Aziz, David N. Parente, Victoria Cheung, Suneil Khanna, Yoo-Joung Ko, Wondwossen Kidanewold, Michael A. Ko, Kelsie L. Thu, and Ju-Yoon Yoon.

EGFR gene status	Asian patient		White, Caucasian	
	Mutant	Wild-type	Mutant	Wild-type
Pre-test probability	0.5	0.5	0.1	0.9
Negative PCR	0.1	~1	0.1	~1
Joint probability	0.05	~0.5	0.01	~0.9
Posterior probability	~0.09	~0.91	~0.01	~0.99
(Residual) Risk	~1:9		~1:90	

Table 1. Risk of false-negative *EGFR* results in a patient with NSCLC, based on ethnicity; courtesy of Yunting Liu, Steven Shen, Manav Shukla, Janet Malowany, Shaheed Hakim, Zared Aziz, David N. Parente, Victoria Cheung, Suneil Khanna, Yoo-Joung Ko, Wondwossen Kidanewold, Michael A. Ko, Kelsie L. Thu, and Ju-Yoon Yoon.

Abbreviations: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PCR: polymerase chain reaction.

and near-perfect specificity for *EGFR* PCR assays, the risk of a false-negative result is estimated to be ~1:9 for an Asian patient and ~1:90 for a white, Caucasian patient (**Table 1**).

Among the 181 patients in our cohort with known *EGFR* status, alterations were identified in 45 (24.9%). Based on the racial composition of our cohort—and assuming that non-Asian patients were predominantly white—the expected prevalence of *EGFR* alterations would be approximately 14.4% (26/181). NGS was performed in 20 patients, with *EGFR* alterations detected in five patients. Among the 161 patients who did not undergo NGS, PCR testing identified *EGFR* mutations in 7 of 21 (33.3%) patients of Asian background, a rate not statistically different from the expected 50% (two-tailed Chi-square $p=0.1899$).

ALK rearrangements have been reported in approximately 5% of NSCLC cases.¹⁰ In our cohort, *ALK* gene rearrangements were identified in 3 of 176 patients (1.7%) who underwent *ALK* IHC testing, which was significantly lower than the expected frequency (two-tailed Chi-square $p=0.0401$). Previous studies have reported a sensitivity of roughly 90% for detecting *ALK* rearrangements by IHC;^{11,12} thus, some rearrangements may have been missed by using IHC alone as a screening modality. *ROS1* gene rearrangement was identified in 1 of 42 tested patients (2.4%), a frequency consistent with published estimates of 1–2%.^{13,14}

Discussion

We observed robust implementation of *EGFR*, *ALK*, and PD-L1 biomarker testing during our study period, primarily through PCR-based assays and IHC with or without FISH. However, *ROS1* IHC testing was only introduced in the latter half of the study window. Broad molecular profiling using NGS panels was limited to the final year of the study period. In 2021, Ontario Health–Cancer Care Ontario (OH-CCO) expanded biomarker testing at diagnosis to include NGS as the first line platform, replacing single-gene testing. The pattern of biomarker testing observed at our institution closely mirrors the provincial funding model in Ontario for NSCLC. Although our testing for *EGFR*, *ALK*, and PD-L1 aligned with the 2017 NCCN recommendations, those guidelines also included *ROS1* and NGS testing, highlighting a significant delay in the implementation of comprehensive biomarker strategies in Ontario compared to U.S. centres. Of the 215 patients in our adenocarcinoma/adenosquamous cohort, based on known prevalence of *ROS1* (~1–2%),^{13,14} *MET* exon 14 skipping (~3–4%),^{15,16} *RET* rearrangements (~1–2%),¹⁷ and given that 195 patients did not receive NGS testing during the study period, these targetable genetic alterations may have been missed in roughly ~10–16 (~5–8%) of patients in the cohort.

An important consideration when selecting a biomarker testing modality is the difference in analytic sensitivity. PCR-based detection of

EGFR mutations is highly sensitive and can also be applied to liquid biopsy samples.^{18,19} While differences between PCR and NGS platforms have been well described, we did not observe overt evidence of negative impact in our limited cohort. However, the lack of statistical significance is likely attributable to sample size constraints. The potential risk of false-negative results remains, particularly among patients of Asian ancestry, in whom *EGFR* mutation prevalence is higher.

Our findings related to *ALK* rearrangement suggest a lower-than-expected detection rate, raising the possibility that test sensitivity may have contributed. While the reported sensitivity of *ALK* IHC is high (~90%),^{11,12} the use of IHC alone—as opposed to upfront FISH or RNA sequencing—may not fully account for the discrepancy.

The estimated risks of false-negative *EGFR* results presented in **Table 1** are based solely on racial background; however, these risks are further modulated by additional clinical factors, such as smoking history. Moreover, driver mutations in lung adenocarcinoma are generally mutually exclusive.²⁰ For example, a patient whose NGS-based tumour testing identifies a *KRAS* p.G12C mutation would have a near-zero probability of also harbouring an *EGFR* mutation. The primary advantage of NGS lies in its ability to comprehensively identify mutually exclusive oncogenic drivers, thereby minimizing the risk of false-negative or false-positive results. This also underscores the importance of re-testing in cases where initial diagnostic material is inadequate for NGS.

Conclusion

In summary, this retrospective study outlines real-world patterns in NSCLC biomarker testing at a Canadian academic centre during a period of evolving provincial funding policy. While guideline-concordant testing for *EGFR*, *ALK*, and PD-L1 was well established, the delayed implementation of *ROS1* and NGS testing reflects systemic barriers to comprehensive molecular profiling. Our findings highlight the importance of equitable access to broad-panel testing and underscore the limitations of single-gene assays, particularly in ethnically diverse populations. Ongoing efforts to standardize testing practices across jurisdictions will be critical for optimizing precision oncology in lung cancer care.

Correspondence

Ju-Yoon Yoon, MD, PhD, MSc, FRCPC
Email: jyoon@sharedhealthmb.ca

Financial Disclosures

All Authors: None declared.

References

1. Riely GJ, Wood DE, Ettinger DS, Aisner DL, Akerley W, Bauman JR, et al. Non-Small Cell Lung Cancer, Version 4.2024, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2024;22(4):249-74.
2. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15(4):504-35.
3. Hirsch FR, Bunn PA, Jr. EGFR testing in lung cancer is ready for prime time. *Lancet Oncol*. 2009;10(5):432-3.
4. Ogino S, Wilson RB. Bayesian analysis and risk assessment in genetic counseling and testing. *J Mol Diagn*. 2004;6(1):1-9.

5. Ogino S, Wilson RB. Genetic testing and risk assessment for spinal muscular atrophy (SMA). *Human Genetics*. 2002;111(6):477-500.
6. Yoon J-Y, Rosenbaum JN, Vergara N, Cohen RB, Wilson RB. Bayesian approach to interpreting somatic cancer sequencing data: a case in point. *Journal of clinical pathology*. 2020.
7. Reinersman JM, Johnson ML, Riely GJ, Chitale DA, Nicastri AD, Soff GA, et al. Frequency of EGFR and KRAS mutations in lung adenocarcinomas in African Americans. *J Thorac Oncol*. 2011;6(1):28-31.
8. Cote ML, Haddad R, Edwards DJ, Atikukke G, Gadgeel S, Soubani AO, et al. Frequency and type of epidermal growth factor receptor mutations in African Americans with non-small cell lung cancer. *J Thorac Oncol*. 2011;6(3):627-30.
9. Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. *Clin Cancer Res*. 2006;12(24):7232-41.
10. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010;363.
11. Rosenbaum JN, Bloom R, Forsyth JT, Hiken J, Armstrong JR, Branson J, et al. Genomic heterogeneity of ALK fusion breakpoints in non-small-cell lung cancer. *Mod Pathol*. 2018;31(5):791-808.
12. Wynes MW, Sholl LM, Dietel M, Schuurin E, Tsao MS, Yatabe Y, et al. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. *J Thorac Oncol*. 2014;9(5):631-8.
13. Dugay F, Llamas-Gutierrez F, Gournay M, Medane S, Mazet F, Chiforeanu DC, et al. Clinicopathological characteristics of ROS1- and RET-rearranged NSCLC in caucasian patients: Data from a cohort of 713 non-squamous NSCLC lacking KRAS/EGFR/HER2/BRAF/PIK3CA/ALK alterations. *Oncotarget*. 2017;8(32):53336-51.
14. Kim HR, Lim SM, Kim HJ, Hwang SK, Park JK, Shin E, et al. The frequency and impact of ROS1 rearrangement on clinical outcomes in never smokers with lung adenocarcinoma. *Ann Oncol*. 2013;24(9):2364-70.
15. Champagnac A, Bringuier PP, Barritault M, Isaac S, Watkin E, Forest F, et al. Frequency of MET exon 14 skipping mutations in non-small cell lung cancer according to technical approach in routine diagnosis: results from a real-life cohort of 2,369 patients. *J Thorac Dis*. 2020;12(5):2172-8.
16. Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shivdasani P, et al. MET Exon 14 Mutations in Non-Small-Cell Lung Cancer Are Associated With Advanced Age and Stage-Dependent MET Genomic Amplification and c-Met Overexpression. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016;34(7):721-30.
17. Wang R, Hu H, Pan Y, Li Y, Ye T, Li C, et al. RET Fusions Define a Unique Molecular and Clinicopathologic Subtype of Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*. 2012;30(35):4352-9.
18. Asano H, Toyooka S, Tokumo M, Ichimura K, Aoe K, Ito S, et al. Detection of EGFR gene mutation in lung cancer by mutant-enriched polymerase chain reaction assay. *Clin Cancer Res*. 2006;12(1):43-8.
19. Wang X, Gao Y, Wang B, Zhang Z, Liang C, Feng H, et al. Analytic and Clinical Validation of an Ultrasensitive, Quantitative Polymerase Chain Reaction Assay for EGFR Mutation Analysis With Circulating Tumor DNA. *Archives of Pathology & Laboratory Medicine*. 2017;141(7):978-84.
20. Collisson EA, Campbell JD, Brooks AN, Berger AH, Lee W, Chmielecki J, et al. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511(7511):543-50.

About the Author



Mariam Jafri, MBChB (Hons), MRCP(UK), BMedSc, MSc, Ph.D

Dr. Mariam Jafri is a medical oncologist and a Senior Investigator at Canadian Cancer Trials Group. Her clinical and research interests are sarcoma, GU cancers and adolescent and young adult cancers. In addition to her medical degree and specialist training in medical oncology, she has PhD in molecular characteristics of renal cancer and related disorders.

Affiliations: Assistant Professor, Department of Oncology, Queen's University, Kingston, Ontario

Current Issues in the Management of Sporadic Non-clear Cell Renal Cell Carcinoma (Non-ccRCC)

Mariam Jafri, MBChB (Hons), MRCP(UK), BMedSc, MSc, Ph.D

Introduction

Renal cell carcinoma (RCC) is the 10th most common cancer type in Canada. Numerous developments in the management of RCC over the last decade have led to improved outcomes, though these have mostly focused on the ~80% of patients with clear cell renal cell carcinoma (ccRCC). The remaining 20% of cases are labelled non-clear cell renal cell carcinoma (non-ccRCC) and represent a biologically and clinically heterogeneous group of diseases that are rare entities.¹ Historically, non-ccRCC has been managed similarly to clear cell tumours. Localized non-ccRCC has better outcomes than ccRCC²; however, survival of metastatic non-ccRCC is inferior to ccRCC (median overall survival [OS] of metastatic non-ccRCC reported as 39.2 months compared to 81.1 months for ccRCC).³

This has led to interest within the RCC scientific and patient communities to further improve outcomes for patients with non-ccRCC. This article describes the current management of patients with non-ccRCC and discusses future areas of interest in the field.

Molecular Classification of Non-clear Cell RCC

Non-ccRCC represents a group of rare, distinct diseases with differing characteristics, as reflected by the World Health Organization (WHO) Classification of Renal Tumors published in 2022.⁴ The WHO has separated non-ccRCC into 6 distinct groups: papillary renal cell carcinoma, oncocytic and chromophobe renal tumours, collecting duct carcinoma, other renal tumours, and molecularly defined tumours.⁵ Molecularly defined tumours comprise 11 subtypes, including *TFE3*-3-rearranged RCC, *TFEB*-altered RCC, *ELOC*-mutated RCC and fumarate hydratase-deficient RCC. The most common subtypes of non-ccRCC are papillary RCC (10–15%), chromophobe RCC (5%), and collecting duct (1%), medullary (1%), and translocation-associated tumours (1–4%).³ Papillary RCC are associated with *MET* alterations, chromophobe RCC are associated with *TP53*, *PTEN*, and *TERT* alterations. Some non-ccRCC subtypes have a worse prognosis, such as *SMARCB1*-deficient medullary RCC or collecting duct RCC.¹

The evidence base for management of specific tumours is limited due to a paucity of trial data. Therefore, these represent orphan tumours, and patients with these tumours would be best managed either within large-volume centres or within clinical trials.

Oncological Management of Early Non-ccRCC

Less than 2%⁶ of patients have metastatic disease at diagnosis; however, 20–40% of patients recur after surgical excision. Recurrence is most likely after the first 5 years and can be predicted using the International Metastatic RCC Database Consortium (IMDC) Risk Stratification criteria for metastatic disease. The IMDC Risk Stratification has been validated in papillary and chromophobe carcinomas.

To reduce the risk of relapse, pembrolizumab is licensed in the adjuvant setting for patients at high risk of recurrence (including patients with pT4 tumours, lymph node involvement, high-grade tumours, and the presence of sarcomatoid lesions). Data from the KEYNOTE-564 trial⁷, which included only patients with cc-RCC, demonstrated an improvement in 48-month OS from 86% in the placebo group to 91.2% in the pembrolizumab group ($p=0.005$). Uptake of pembrolizumab in Canada is limited to patients with ccRCC due to a lack of data and federal funding for the use of pembrolizumab in non-ccRCC.

The EVEREST trial included a subgroup of non-ccRCC (109 patients with papillary RCC and 99 with chromophobe RCC) at high risk of relapse following nephrectomy.⁸ This trial evaluated everolimus versus placebo and did not detect an improvement in recurrence-free survival (RFS) or OS in non-ccRCC. There were unsurprisingly significantly higher levels of grade 3 toxicity with everolimus vs. placebo. Thus, everolimus is not recommended in the adjuvant setting for non-ccRCC.

The PROSPER-RCC trial included a cohort of patients with non-ccRCC and evaluated neoadjuvant nivolumab with surveillance alone.⁹ The trial was curtailed early for futility, indicating there is no data supporting adjuvant nivolumab in non-ccRCC.

Despite the licensing of pembrolizumab in all RCC subgroups with intermediate or high risk of relapse, the role of pembrolizumab in non-cc-RCC remains unclear. This is therefore an area for research and clinical trials. These datasets

have led some to believe that adjuvant treatment in non-ccRCC is a data desert and that adjuvant treatment should not be offered to patients with non-ccRCC outside of a clinical trial.¹

Management of Metastatic RCC

Much of the data regarding the management of non-ccRCC is derived from trials that predominantly evaluated ccRCC. The PAPMET trial, which included Canadian sites through the Canadian Cancer Trials Group (CCTG), evaluated tyrosine kinase inhibitors (TKI) in papillary RCC.¹⁰ Papillary RCC are associated with upregulated *MET* signalling and thus TKI are of interest. Patients from Canada and the US with papillary RCC were randomized to receive either sunitinib as standard of care or cabozantinib, crizotinib, or savolitinib. Progression-free survival (PFS) was the primary outcome measure, and the savolitinib and crizotinib arms were closed early due to pre-defined futility. PFS was significantly higher in the cabozantinib group (9 months) than in the sunitinib group (5.6 months). Updated survival analysis from PAPMET indicated no significant increase in survival for those treated with cabozantinib compared with sunitinib.¹¹ However, this trial provides the only randomized data for treatment options in papillary RCC.

KEYNOTE-B61 was a single-arm trial in non-ccRCC evaluating lenvatinib and pembrolizumab in 158 patients.¹² This trial demonstrated a 49% objective response rate (ORR), a 12-month PFS of 63%, and an OS of 82%. Recently published 2-year follow-up data demonstrated a 51% ORR, with 13 patients having a complete response and 67% a partial response. The duration of response was 19.5 months across all subtypes.¹³ Toxicity was as expected from immunotherapy and TKI combinations. The results were consistent across different histologies and with other trials involving checkpoint inhibitors. For example, KEYNOTE-427 evaluated single-agent pembrolizumab in 3 weekly doses for up to 24 months in non-ccRCC.¹⁴ This trial demonstrated an ORR of 26.7%, and 59.7% of patients had a duration of response that lasted more than 12 months. The median PFS was 4.2 months, and the median OS was 28.9 months.

A single-centre study from Memorial Sloan Kettering evaluated 47 patients with non-ccRCC who were treated with nivolumab and cabozantinib.¹⁵ This combination treatment was associated with an ORR of 47% in the

Subtype	Type of Treatment	Potential options
Papillary	- Targeted treatment - mTOR inhibitors - Immunotherapy - Combination strategies	- cabozantinib, savitinib, - everolimus, temsirolimus - pembrolizumab, nivolumab - pembrolizumab + axitinib, nivolumab + cabozantinib, nivolumab + ipilimumab, lenvatinib + pembrolizumab - erlotinib and Bevacizumab in non-FH deficient papillary RCC
Chromophobe	- Targeted treatment - mTOR inhibition - Combination strategies	- Sunitinib - everolimus, temsirolimus - pembrolizumab + axitinib, nivolumab + Cabozantinib
Collecting duct tumours	Chemotherapy	gemcitabine + cisplatin/carboplatin, paclitaxel + carboplatin
SMARCB1-deficient renal medullary carcinoma	Chemotherapy	Platinum-based chemotherapy

Table 1. Management Options in non-ccRCC based on subtype; *summarized from Nepali et al.*²⁸

cohort, including papillary RCC, unclassified, or translocation-associated RCC. In the cohort consisting of patients with chromophobe RCC, no responses were identified. This indicates a differential response dependent on histology. A cohort of patients with non-ccRCC treated with ipilimumab and pembrolizumab was evaluated as part of the CheckMate 920 trial,¹⁶ and no new safety signals were identified. Fifty-two patients were evaluated, of whom 42.3% had unclassified histology, 34.6% papillary, 13.5% chromophobe, 3.8% translocation-associated, 3.8% collecting duct, and 1.9% renal medullary tumours. The ORR in this cohort was 19.6%, with a 12-month PFS of 22.7%. Recently, the DRON1 retrospective multicentre study evaluated immunotherapy and checkpoint inhibitor combinations in 56 centres in 17 countries. This study evaluated lenvatinib and pembrolizumab, pembrolizumab and axitinib, nivolumab and cabozantinib, and ipilimumab and nivolumab. The ORR were significantly higher for lenvatinib and pembrolizumab ($p=0.047$), and it appeared response rates were lowest for ipilimumab and nivolumab.¹⁷

SUNNIFORECAST¹⁸ is a recently reported phase II trial assessing ipilimumab and nivolumab versus the physician's choice of treatment, which were overwhelmingly TKI options. The 12-month OS was significantly higher in the ipilimumab and nivolumab arm compared to TKI (78% vs. 68%). The ORR was also significantly higher in the experimental arm than the standard of care (33% vs. 20%). This trial suggested that

the ipilimumab and nivolumab combination is an attractive option in non-ccRCC.

Current National Clinical Trials Network (NCTN) guidelines recommend cabozantinib as a single agent, cabozantinib and nivolumab, or lenvatinib and pembrolizumab as first-line agents in non-ccRCC. There is no current data to determine the best of these options in this setting.

The current Canadian guidelines suggest a personalized approach, reflecting the differential outcomes observed for the various subtypes.¹ **Table 1** summarizes potential treatment options for non-ccRCC. For patients with *de novo* metastatic papillary and chromophobe RCC, cytoreduction is recommended based on data from ccRCC. Furthermore, in these subtypes, it is recommended that localized techniques, such as surgery, radiofrequency ablation, and radiotherapy techniques such as stereotactic ablative radiotherapy, be considered for patients with oligometastatic disease (5 or fewer metastases). Surveillance is the recommended treatment option for individuals with low-volume/favourable-risk papillary and chromophobe RCC, as these conditions can be indolent.

Canadian guidelines for symptomatic/high-volume RCC reflect the National Comprehensive Cancer Network (NCCN) guidelines - recommending cabozantinib as a single agent or a checkpoint inhibitor in combination with a TKI. For those with metastatic chromophobe carcinoma, given the absence of

trial data supporting interventions in this setting, recruitment into clinical trials is recommended.¹

Specific Subsets of Non-ccRCC

Chromophobe RCC generally has a good prognosis and has not been found to be impacted by risk factors such as obesity and smoking. Up to 10% of cases will metastasize, with a subset having sarcomatoid differentiation, which is associated with poor prognosis. Chromophobe RCC generally has poor response rates, with limited data available on treatment efficacy. However, a single-arm, phase II study evaluated the combination of lenvatinib with everolimus in patients with newly diagnosed non-ccRCC. Among nine patients with chromophobe RCC, the ORR was 44% with the combination. The lenvatinib/pembrolizumab study included more patients with chromophobe RCC (29 patients) and the ORR within this subset was 28%.

SMARCB1-deficient RCC is a rare, aggressive subtype with poor outcomes, representing <1% of RCC. MD Anderson has published the largest series of *SMARCB1*-deficient RCC cases. These tumours are associated with sickle hemoglobinopathies and are more frequent in males. The authors of this publication recommends platinum-based chemotherapy, such as carboplatin and paclitaxel, in the first line, followed by gemcitabine and doxorubicin or erlotinib.¹⁹ Immunotherapy has not been shown to be beneficial for this population.¹

Collecting duct tumours represent around 1% of RCC, and over 50% of patients with collecting duct tumours have metastatic disease. Patients with metastatic collecting duct tumours have a median OS of 7 months.²⁰ Given their rarity, data regarding the optimal management is limited. The GETUG phase II trial evaluated 23 patients with collecting duct tumours and found that gemcitabine and cisplatin treatment was associated with a PFS of 7.1 months and an OS of 10.5 months.²¹ These data suggested that gemcitabine and cisplatin can be used to treat metastatic collecting duct tumours.¹

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is associated with inherited fumarate hydratase (*FH*) mutations. Srinivasan et al. published a phase II trial assessing bevacizumab and erlotinib in 43 patients with HLRCC and 40 patients with sporadic papillary RCC.²² The ORR was 72% with HLRCC-associated papillary renal-cell carcinoma, the median PFS

was 21.1 months (95% CI: 15.6–26.6), and the median OS was 44.6 months (95% CI: 32.7–not estimated). A confirmed response occurred in 14 patients (35%; 95% CI: 22–51) with sporadic papillary renal-cell carcinoma (those without *FH* mutations), with a median PFS of 8.9 months (95% CI: 5.5–18.3) and a median OS of 18.2 months (95% CI: 12.6–29.3). These data have led to the inclusion of this combination of erlotinib and bevacizumab in HLRCC in the NCCN guidelines.

A retrospective study of non-ccRCC from China was presented at the American Society of Clinical Oncology's annual Genitourinary Cancers Symposium (ASCO GU).²³ This study evaluated 77 patients, including 70 HLRCC cases and seven case with somatic *FH*-loss. Recurrent pathogenic alterations were found in *NF2* (6/57, 11%), *CDH1* (6/57, 11%), *PIK3CA* (6/57, 11%), and *TP53* (5/57, 8.8%) genes. Sixty-seven patients were evaluable for response to first-line systemic therapy with bevacizumab and erlotinib (n=12), TKI monotherapy (n=29), or immune checkpoint inhibitor (ICI)/TKI (n=26). ICI/TKI combination therapy was associated with a more favourable OS (hazard ratio [HR]: 0.19, 95% CI: 0.04–0.90) and PFS as first-line therapy (HR: 0.22, 95% CI: 0.07–0.71) compared to bevacizumab and erlotinib combination therapy. This led to a phase II single centre trial in China evaluating lenvatinib plus tislelizumab, which was presented at ASCO GU in 2025.²⁴ Seventeen patients with either germline *FH* mutations or bilallelic somatic *FH* mutations were included in the study. The ORR in this study was 93% with a 20% complete response rate, suggesting this combination requires further study.

Future Developments

The benefit of adjuvant pembrolizumab in non-ccRCC remains unclear despite FDA approval in this setting, emphasizing the need for further clinical trials. The RAMPART study will provide important information on the role of durvalumab with or without tremelimumab across several cancer subtypes. This trial includes an active surveillance arm.²⁵

In the metastatic setting, there is a concerted effort to improve outcomes as non-ccRCC has been somewhat neglected compared to ccRCC. There have been single-arm phase II trials such as KEYNOTE-B61; however, single-arm trials do

not produce data of sufficient quality to change practice. The SAMETA trial evaluates durvalumab versus durvalumab and sunitinib versus sunitinib alone versus durvalumab alone.²⁶ PAPMET-2 also combines immunotherapy (atezolizumab) with cabozantinib compared to cabozantinib alone, using PFS as an endpoint.²⁷ Both these trials are currently accruing patients. Given the relative lack of developments in non-ccRCC, other treatments are being considered. CCTG is developing a phase I trial in non-ccRCC assessing chimeric antigen receptor (CAR) T-cell therapy directed against GPNMB-1, as this protein is overexpressed in some types of non-ccRCC. Other areas of interest in non-ccRCC are determining genomic, proteomic, transcriptomic, or metabolomic signatures to enable personalized prognostication, treatment, and follow-up of non-ccRCC.

Conclusion

Outcomes of non-ccRCC remain poor compared to ccRCC, and robust data to help make clinical decisions are lacking. Management of non-ccRCC is challenging due to their heterogeneous clinical and biological behaviour. Personalized medicine involving assessment of genetic alterations and the tumour microenvironment is of particular interest in non-ccRCC. A better understanding of these factors may enable the development of novel treatments. Currently, it is strongly recommended that patients with non-ccRCC participate in clinical trials to strengthen the evidence base for therapeutic interventions.

Correspondence

Mariam Jafri, MBChB (Hons), MRCP(UK), BMedSc, MSc, Ph.D

Email: mjafr@ctg.queensu.ca

Financial Disclosures

M.J.: None declared.

References

1. Graham J, Ahmad AE, Basappa NS, Bernhard JC, Bhindi B, Bossé D, et al. 2024 CUA-KCRNC Expert Report: Management of non-clear cell renal cell carcinoma. *Can Urol Assoc J*. 2024;18(11):E371-e86.
2. Gulati S, Philip E, Salgia S, Pal SK. Evolving treatment paradigm in metastatic non clear cell renal cell carcinoma. *Cancer Treat Res Commun*. 2020;23:100172.
3. Urman D, Deshler L, Weise N, Shabaik A, Derweesh I, Bagrodia A, et al. Outcomes of patients with advanced renal cell carcinoma with non-clear cell histology treated with systemic therapy. *Clin Genitourin Cancer*. 2023;21(6):660-8.e1.
4. Goswami PR, Singh G, Patel T, Dave R. The WHO 2022 Classification of renal neoplasms (5th Edition): Salient updates. *Cureus*. 2024;16(4):e58470.
5. Moch H, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, et al. The 2022 World Health Organization Classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. *Eur Urol*. 2022;82(5):458-68.
6. Cardenas LM, Sigurdson S, Wallis CJD, Lalani A-K, Swaminath A. Advances in the management of renal cell carcinoma. *CMAJ*. 2024;196(7):E235-E40.
7. Powles T, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2022;23(9):1133-44.
8. Gulati S, Tangen C, Ryan CW, Vaishampayan UN, Shuch BM, Barata PC, et al. Adjuvant everolimus in non-clear cell renal cell carcinoma: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2024;7(8):e2425288-e.
9. Allaf ME, Kim S-E, Master V, McDermott DF, Harshman LC, Cole SM, et al. Perioperative nivolumab versus observation in patients with renal cell carcinoma undergoing nephrectomy (PROSPER ECOG-ACRIN EA8143): an open-label, randomised, phase 3 study. *Lancet Oncol*. 2024;25(8):1038-52.
10. Pal SK, Tangen C, Thompson IM, Jr., Balzer-Haas N, George DJ, Heng DY, et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet*. 2021;397(10275):695-703.
11. Barata P, Tangen C, Plets M, Thompson IM, Narayan V, George DJ, et al. Final Overall survival analysis of S1500: a randomized, phase ii study comparing sunitinib with cabozantinib, crizotinib, and savolitinib in advanced papillary renal cell carcinoma. *J Clin Oncol*. 2024;42(33):3911-6.

12. Albiges L, Gurney H, Atduiev V, Suarez C, Climent MA, Pook D, et al. Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, phase 2 trial. *Lancet Oncol.* 2023;24(8):881-91.
13. Voss MH, Gurney H, Atduiev V, Suarez C, Climent MA, Pook D, et al. First-line pembrolizumab plus lenvatinib for advanced non-clear-cell renal cell carcinoma: updated results from the phase 2 KEYNOTE-B61 trial. *Eur Urol.* 2025.
14. McDermott DF, Lee JL, Ziobro M, Suarez C, Langiewicz P, Matveev VB, et al. Open-label, single-arm, phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. *J Clin Oncol.* 2021;39(9):1029-39.
15. Lee C-H, Voss MH, Carlo MI, Chen Y-B, Zucker M, Knezevic A, et al. Phase II trial of cabozantinib plus nivolumab in patients with non-clear-cell renal cell carcinoma and genomic correlates. *J Clin Oncol.* 2022;40(21):2333-41.
16. Tykodi SS, Gordan LN, Alter RS, Arrowsmith E, Harrison MR, Percent I, et al. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. *J Immunother Cancer.* 2022;10(2).
17. Massari F, Mollica V, Kopp RM, Grande E, Fiala O, Kanesvaran R, et al. Immune-based combinations in intermediate-/poor-risk patients with non-clear cell renal cell carcinoma: results from the ARON-1 study. *Eur Urol Focus.* 2025.
18. Bergmann L, Albiges L, Ahrens M, Gross-Goupil M, Boleti E, Gravis G, et al. Prospective randomized phase-II trial of ipilimumab/nivolumab versus standard of care in non-clear cell renal cell cancer - results of the SUNNIFORECAST trial. *Ann Oncol.* 2025;36(7):796-806.
19. Lebenthal JM, Kontoyiannis PD, Hahn AW, Lim ZD, Rao P, Cheng JP, et al. Clinical Characteristics, Management, and Outcomes of Patients with Renal Medullary Carcinoma: A Single-center Retrospective Analysis of 135 Patients. *Eur Urol Oncol.* 2025;8(2):315-23.
20. Suarez C, Marmolejo D, Valdivia A, Morales-Barrera R, Gonzalez M, Mateo J, et al. Update in collecting duct carcinoma: Current aspects of the clinical and molecular characterization of an orphan disease. *Front Oncol.* 2022;12:970199.
21. Oudard S, Banu, E, Vieillefond, A, Fournier, L, Priou, F, Medioni, J, Culine, S. Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Genitales) Study. *J Urol.* 2007;177:1698-702.
22. Srinivasan R, Gurram S, Singer EA, Sidana A, Al Harthy M, Ball MW, et al. Bevacizumab and erlotinib in hereditary and sporadic papillary kidney cancer. *N Engl J Med.* 2025;392(23):2346-56.
23. Xu Y, Kong W, Cao M, Wang J, Wang Z, Zheng L, et al. Genomic Profiling and Response to immune checkpoint inhibition plus tyrosine kinase inhibition in FH-deficient renal cell carcinoma. *Eur Urol.* 2023;83(2):163-72.
24. Kong W, Wu G, Xu Y, Wang Z, Zhang J. Lenvatinib plus tislelizumab as first-line therapy for advanced fumarate hydratase-deficient renal cell carcinoma: A single-center, single-arm, phase II study. *J Clin Oncol.* 2025;43(5_suppl):443-.
25. Oza B, Frangou E, Smith B, Bryant H, Kaplan R, Choodari-Oskoei B, et al. RAMPART: A phase III multi-arm multi-stage trial of adjuvant checkpoint inhibitors in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse. *Contemp Clin Trials.* 2021;108:106482.
26. Choueiri TK, Xu W, Poole L, Telaranta-Keerie A, Hartmaier R, Powles T. SAMETA: An open-label, three-arm, multicenter, phase III study of savolitinib + durvalumab versus sunitinib and durvalumab monotherapy in patients with MET-driven, unresectable, locally advanced/metastatic papillary renal cell carcinoma (PRCC). *J Clin Oncol.* 2022;40(16_suppl):TPS4601-TPS.
27. Maughan BL, Plets M, Pal SK, Ged Y, Tangen C, Vaishampayan UN, et al. SWOG S2200 (PAPMET2): A phase II randomized trial of cabozantinib with or without atezolizumab in patients with advanced papillary renal cell carcinoma (PRCC). *J Clin Oncol.* 2024;42(4_suppl):TPS493-TPS.
28. Nepali PR, Eraky A, Okhawere KE, Dogra N, Mehrazin R, Badani K, et al. Molecular and therapeutic landscape of non-clear cell renal carcinoma. *Nat Rev Urol.* 2025.



Canadian Oncology Today
Science for the Real World

canadianoncologytoday.com

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

© 2025 Canadian Oncology Today.

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

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

