Canadian Oncology Today

Volume 3, Issue 1

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

Spring 2026

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

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

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**.

About the Authors

Vladimir Djedovic, MD, MSc, FRCPC

Dr. Vladimir Djedovic is currently a fifth year medical oncology resident at the University of Ottawa. He holds a Master of Science degree in Physiology from the University of Toronto. His clinical and research interests are primarily in gastrointestinal and genitourinary oncology with plans to pursue fellowship training following completion of his residency.

Affiliations: University of Ottawa; The Ottawa Hospital; Ottawa, ON

Donald Bastin, MD, MSc

Dr. Donald Bastin is currently a Medical Oncology resident at the University of Ottawa. He completed his Internal Medicine residency at the University of Ottawa, his MD at Western University in London, ON, and his MSc at McMaster University in Hamilton, ON. His primary research interests are in immuno-oncology and translation of basic science discoveries from bench to bedside.

Affiliations: University of Ottawa; The Ottawa Hospital; Ottawa, ON

Michael Vickers, MD, MPH, FRCPC

Dr. Vickers completed medical school at Memorial University in Newfoundland in 2004, followed by Internal Medicine and Medical Oncology residencies at the University of Calgary. He then completed a Clinical/Research Fellowship in Gastrointestinal Oncology at the University of Ottawa followed by a Masters of Public Health at the Harvard School of Public Health in 2014. From 2010-2014 he practiced at the Tom Baker Cancer Centre in Calgary and has been a Medical Oncologist at The Ottawa Hospital Cancer Centre since 2014, specializing in GI cancers as well as head & neck cancers, cancers of unknown primary and neuroendocrine tumours. His primary focus of research is anorectal cancers and neuroendocrine tumours.

Affiliations: University of Ottawa; The Ottawa Hospital; Ottawa, ON

doi.org/10.58931/cot.2026.3144

The Management of Advanced Anal Squamous Cell Carcinoma

Vladimir Djedovic, MD, MSc, FRCPC
Donald Bastin, MD, MSc
Michael Vickers, MD, MPH, FRCPC

Introduction

Cancers of the anal canal are rare malignancies defined anatomically from the anorectal junction to the perianal region.[1,2] The most common histotype is anal squamous cell carcinoma (ASCC), which represents 1%–2% of all gastrointestinal cancers.[1] Despite recent advances in the treatment of modifiable risk factors, the incidence of ASCC continues on a slow but unabated upward trajectory driven by predisposing factors including smoking, human papillomavirus (HPV) and human immunodeficiency virus (HIV) infections, and immunosuppression, amongst others.[1,2] Metastatic ASCC (mASCC), either *de novo* stage IV disease or distant recurrence following definitive concurrent chemoradiation, is also increasing in frequency, representing 10%-30% of all diagnoses.[1,2] While localized disease is curable with chemoradiation, using mitomycin-c and fluoropyrimidine-based sensitizing chemotherapy, advanced or metastatic disease is associated with significantly worse outcomes and a historical median overall survival (OS) below 20 months and 5-year OS between 19%–30%.[3,4] The management of advanced or metastatic ASCC has undergone significant changes in the past decade, and herein we will highlight the current treatment paradigm and future directions in this field.

Overview of Advanced ASCC Treatment in the First-line Setting

Owing to the relative rarity of advanced ASCC and the consequent difficulty enrolling patients into randomized trials, there have historically been few treatment options with robust prospective data in this setting. Available options were extrapolated from other squamous cell carcinomas (SCCs), retrospective case series, and small single-arm phase II trials.[5-11] Platinum-based combinations, typically cisplatin with 5-fluorouracil (5-FU), were commonly used, albeit with moderate objective response rates (ORR) ranging from 30%-60%, limited duration of response (DOR), and often significant toxicities including neuropathy, myelosuppression, febrile neutropenia, and mucositis, requiring frequent dose-modifications or treatment interruptions.[5-11] Overall, the combination of poor patient tolerance, limited OS, and scarce prospectively validated regimens led to international collaborations for the development of subsequent clinical trials.

In 2020, the International Rare Cancers Initiative Anal Cancer Working Group conducted the landmark InterAAct trial. This was an international, prospective, randomized, phase II study of 91 previously untreated patients with advanced or mASCC, comparing 5-FU and cisplatin versus carboplatin and paclitaxel in a pick-the-winner design with ORR as the primary endpoint.[12] While no difference in ORR was detected, as it was 57% (95% confidence interval [CI], 39.4%-73.7%) for cisplatin and 5-FU versus 59% (95% CI, 42.1%-74.4%) for carboplatin and paclitaxel, the carboplatin arm exhibited fewer grade ≥3 adverse events (36% versus 62%; p=0.016), resulted in a numerically superior progression-free survival (PFS) of 8.1 months (95% CI, 6.6-8.6) versus 5.7 months (95% CI, 3.3-9.0) and an OS of 20 months (95% CI, 12.7-not reached) versus 12.3 months (95% CI, 9.2-17.7), with a hazard ratio (HR) of 2.00 (95% CI, 1.15-3.48; p=0.014). Therefore, this trial established carboplatin and paclitaxel as the preferred first-line chemotherapy regimen in this setting.[12]

Building on this, recent efforts have focused on a pathogenesis-informed, biomarker-driven approach to clinical trial development underpinned by improved understanding of ASCC biology.[6] HPV infection is present in >90% of ASCC cases, and carcinogenesis is driven by HPV-16 and HPV-18, which produce viral oncoproteins E6 and

E7 that disrupt p53 and retinoblastoma tumour suppressor functions and promote resultant cell proliferation and genomic instability.[13,14] Despite a relatively low tumour mutational burden, HPV-associated cancers are immunologically "hot", exhibiting dense infiltration of cytotoxic T cells and tumour-infiltrating lymphocytes, transforming growth factor (TGF)-β and interferon (IFN)-ɣ upregulation, increased antigenicity, and higher programmed death ligand 1 (PD-L1) expression.[13,14] Patients living concurrently with HIV and mASCC likewise exhibit an immunophenotype potentially amenable to immunotherapy (IO) treatment, with an increased density of $CD8^+$ T cells in the tumour microenvironment (TME) even when viral replication is suppressed.[13,14] Together, these observations provided the rationale for the use of IO in recent practice-changing clinical trials.

The POD1UM-303/InterAAct-2 trial was a landmark global randomized, controlled, double-blind phase III clinical trial including 308 previously untreated patients with inoperable locally advanced ASCC or mASCC that evaluated the immune checkpoint inhibitor (ICI) retifanlimab (an anti-programmed cell death protein 1 [PD-1] antibody) in addition to carboplatin and paclitaxel versus carboplatin and paclitaxel monotherapy in the first-line setting.[15] Previous chemotherapy concurrent with radiotherapy was permitted in the neoadjuvant/adjuvant setting if completed 6 months or more prior to entry of the study. Notably, in the initial phase II InterAAct trial cohort, of the 45 patients randomized to carboplatin and paclitaxel, 70% were female with median age of 61, and 89% of patients had metastatic rather than locally advanced disease, an Eastern Cooperative

Trial	Patient population	Treatment line	Sample size (N)	Regimen and Comparator	ORR % (95% CI)	Median PFS (months)	Median OS (months)
InterAAct[12]	Metastatic or recurrent ASCC	1L	91	Carboplatin + paclitaxel	59% (42.1-74.4)	8.1	20.0
				Cisplatin + 5-FU	57% (39.4-73.7)	5.7	12.3
POD1UM-303/ InterAAct-2[15]	Metastatic or recurrent ASCC	1L	308	Retifanlimab + carboplatin + paclitaxel	56% (47.6-63.8)	8.3	29.2 (initial publication)
				Carboplatin + paclitaxel	44% (36.2-52.4)	6.2	23.0 (initial publication)
POD1UM-202[21]	Previously treated ASCC	≥2L	94	Retifanlimab (single-arm trial)	13.8% (7.6-22.5)	2.3	10.1
KEYNOTE-158 (ASCC)[22]	Advanced ASCC, PD-L1 not selected	≥2L	112	Pembrolizumab (single-arm trial)	11% (6-18)	2.0	12.0
NCI9673 – Part B[23]	Refractory metastatic ASCC	≥2L	37	Nivolumab ± ipilimumab	24% (15-33)	4.1	11.5

Table 1. Selected Trials on the Management of Advanced ASCC; *courtesy of Vladimir Djedovic, MD, MSc, FRCPC, Donald Bastin, MD, MSc, and Michael Vickers, MD, MPH, FRCPC.*

Abbreviations: 1L: first-line; **2L:** second-line; **ASCC:** anal squamous cell carcinoma; **CI:** confidence interval; **ORR:** objective response rate; **OS:** overall survival; **PD-L1:** programmed death ligand 1; **PFS:** progression-free survival.

Oncology Group performance status (ECOG PS) of 1, and 4% were HIV-positive, with 26 of 45 patients having received induction chemoradiation therapy previously. In the InterAAct-2 study, the cohort was quite similar, with >70% females, a median age of 61, predominantly white Europeans (>90% of the cohort), 82% had metastatic rather than locally recurrent disease, the majority of patients had ECOG PS of 0-1, and 3% were HIV-positive. A notable difference between the trials is that PD-L1 expression testing was performed only in the InterAAct-2 trial and revealed that 91% of patients had PD-L1 expression ≥1, as determined by the SP263 PD-L1 immunohistochemistry assay.

In the InterAAct-2 trial, the primary endpoint was PFS, with OS and safety as key secondary endpoints.[15] The retifanlimab arm had improved PFS, with a median PFS of 9.3 months (95% CI, 7.5-11.3) versus 7.4 months (95% CI, 7.1-7.7), resulting in a HR of 0.63 (95% CI, 0.47-0.84; one-sided p=0.0006). Likewise, the ORR was 55.8% (95% CI, 47.6%-63.8%) versus 44.2% (95% CI, 36.2%-52.4%; p=0.013), and median DOR of 14 months (95% CI, 8.6-22.2) versus 7.2 months (95% CI, 5.6-9.3), all favouring the retifanlimab combination arm.[15] At the time of this publication, the median OS of this study was 32.8 months (95% CI, 24.2-not estimable) versus 22.2 months (95% CI, 15.1-27.9) in the chemotherapy-alone arm, with a HR of 0.70, but these data remain immature.[15] The observed benefits of the combination treatment were contrasted with increased toxicity with the addition of retifanlimab.[15]

The most common toxicities in both study arms of the InterAAct-2 trial were hematologic, with anemia (66% versus 70%), neutropenia (47% versus 44%), and thrombocytopenia (14% versus 20%), in the retifanlimab and placebo arms, respectively. In the experimental arm, there were 83% grade ≥3 adverse events as compared to 75% in the placebo arm, with 4 versus 1 treatment-related deaths.[15] Of note, the discrepancy in serious adverse event rates and treatment-related adverse events appears to be mediated by the immune-related adverse event (irAE) rate (49% versus 26%), which was, as expected, higher in the retifanlimab arm.[15] These adverse events led to an 11% treatment discontinuation rate versus 3% for chemotherapy alone.[15] However, the most common irAEs were reported to be grade 1 or 2 in severity and did not typically lead to dose interruptions, delays, or discontinuation, and included neuropathy (11%), hypothyroidism (14%), diarrhea (10%), hyperthyroidism (8%), pruritis (7%), adrenal insufficiency (5%), and rash (2%).[15]

Despite the irAEs highlighted above, most treatment delays were due to hematologic toxicities, owing to the carboplatin and paclitaxel backbone.[15] The dosing regimen for this protocol is carboplatin AUC 5 on day 1 and paclitaxel 80 mg/m^2 on day 1, 8, and 15 of a 28-day cycle, for up to 6 cycles.[16] However, dose-density can lead to treatment interruptions due to cumulative hematologic toxicities.[15] No prospective trials have compared alternate dosing schedules in this setting, and almost all prospective ASCC trials use the weekly paclitaxel regimen. However, there are small retrospective single-institution data that support the use of carboplatin AUC 5 and paclitaxel 175 mg/m^2 every 3 weeks. One such study by Kim *et al*. included 12 patients with first-line metastatic ASCC and 6 patients with locally advanced and/or pretreated ASCC, from a single-centre tumour registry, and identified an ORR of 53%, including 3 pathologic complete responses, with a median OS of 12.2 months.[16] Data from other cancer types suggest that 3-weekly dosing is less likely to cause treatment delays due to anemia than the dose-dense version, at the expense of potentially increased neuropathy or neutropenia.[16,17] Therefore, for patients with significant anemia leading to treatment delays, alternate dosing (dose reductions or schedule adjustments) of carboplatin and paclitaxel may be beneficial and attempted at the discretion of the treating oncologist.

Overall, despite the added toxicities, OS benefit was generally in favour of the addition of retifanlimab across all predefined subgroups, aside from patients with PD-L1 expression <1%, and those who are HIV-positive, aged ≥75 years, and with locally recurrent disease.[15] It must be acknowledged that, given the small numbers of patients in each of these subgroups (and resultant wide confidence intervals), these data should be interpreted with caution and should not form the basis of treatment allocation decisions and eligibility for retifanlimab. Taken together, the InterAAct-2 trial has established the combination of carboplatin plus paclitaxel with retifanlimab as the preferred first-line standard of care for recurrent or metastatic ASCC. Indeed, this regimen is currently approved by the US Food and Drug Administration (FDA) for this indication. However, at the time of writing, retifanlimab in combination with carboplatin and paclitaxel is pending reimbursement review by

Canada's Drug Agency. Additionally, several larger immunotherapy trials are ongoing for advanced ASCC or mASCC, examining alternative chemotherapy and immunotherapy regimens. Notably, the field is awaiting results from the EA2176 trial, a phase III trial of carboplatin plus paclitaxel with nivolumab (anti-PD-1) in mASCC with PFS as primary endpoint and OS, ORR, and toxicity profile as secondary outcomes in a 2:1 randomization. Further, the SPARTANA trial is evaluating the feasibility of spartalizumab (anti-PD-1) in combination with a docetaxel, cisplatin, 5-FU (DCF) chemotherapy backbone, alongside radiation, to enhance tumour antigen shedding and anti-tumour immune activation.[18,19] These studies may provide feasible alternatives, or improvements, to the current standard of care.

Second-line and/or Platinum-Refractory Therapy

While carboplatin plus paclitaxel with or without retifanlimab remains the most frequently used first-line regimen, there is no established standard of care in the second-line setting, for which cytotoxic chemotherapy, immunotherapy, or participation in clinical trials may be considered. Despite a current lack of large prospective second-line trials for advanced ASCC, likely reflecting disease rarity and the need for a logistically onerous global initiative to enroll sufficient numbers of patients, there are multiple options with established ORRs ranging from 10%-30%, PFS of 2-3 months, and OS estimates of 10-20 months. Treatment decisions need to be individualized in this data-limited space, taking comorbidities, performance status, and patient preferences into consideration. Since chemotherapy trials have been extensively reviewed in other publications, we will summarize key recent IO trials below.[20]

The phase II POD1UM-202 trial assigned 94 previously treated patients with advanced or metastatic ASCC, who were either intolerant of, or progresses following, platinum-based chemotherapy, to receive retifanlimab in the second-line setting.[21] The study reported an ORR of 13.8% (95% CI, 7.6-22.5), with an 1.1% complete response rate, 12.8% partial response rate, and a stable disease rate of 35.1%, resulting in a disease-control rate of 48.9% (95% CI, 38.5-59.5).[21] Median PFS and OS were 2.3 (95% CI, 1.9-3.6) and 10.1 (95% CI, 7.9-not estimable) months, respectively.[21] Safety signals were consistent with prior IO trials. Likewise, the phase II KEYNOTE-158 basket trial evaluated pembrolizumab (anti-PD-1) monotherapy in multiple tumour types.[22] The anal cancer cohort of 112 patients revealed an ORR of 15% (95% CI, 8-25) in PD-L1-positive tumours and 3% (95% CI, 0-17) in PD-L1-negative tumours. The median OS was 11.9 months (95% CI, 9.1-14.9), with a PFS of 2.0 months (95% CI, 2.0-2.1), and the median DOR was not reached at the time of published analysis.[22] Of note, no definitive conclusions could be drawn based on PD-L1 status based on the recorded number of events.[22] Lastly, a 2017 multicentre, single-arm, phase II study investigated nivolumab monotherapy for treatment-refractory mASCC with ORR as the primary endpoint.[23] Of the 37 enrolled patients, 9 (24%) exhibited a therapy response, including 2 complete responses and 7 partial responses.[23] Taken together, these studies suggest a modest benefit for single-agent IO in terms of ORR, OS, and PFS, with a subset of patients (yet to be defined) exhibiting longer-term disease control. Single-agent IO in second- and later-line settings, therefore, represents a modest tool in the limited armamentarium of treatment options and is associated with a relatively favourable risk-benefit ratio. To our knowledge, no jurisdiction in Canada reimburses IO in the refractory setting of advanced ASCC.

Based on evidence from other cancer types, IO treatment intensification has also been assessed in mASCC. The phase II NCI9673 trial part B investigated nivolumab with or without cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibition using ipilimumab in patients with refractory mASCC.[24] The addition of ipilimumab to nivolumab did not improve PFS (2.9 months [90% CI, 1.9-3.8] versus 3.7 months [90% CI, 2.0-5.6]), exhibited similar ORR (17.4% versus 21.5%; p=0.89), and OS (20.0 months versus 15.9 months; p=0.89) compared to nivolumab monotherapy.[24] Further, dual ICI use resulted in significantly higher rates of grade ≥3 adverse events (25% versus 12%), highlighting the need for caution regarding combination ICI treatments in this setting.[24]

Taken together, while there is presently no universally accepted second-line standard of care in mASCC, treatment must be individualized with options including cytotoxic chemotherapy (i.e., folinic acid, fluorouracil, plus oxaliplatin [FOLFOX]; folinic acid, fluorouracil, plus irinotecan [FOLFIRI]; cisplatin plus 5-FU; cisplatin plus mitomycin-c; or single-agent taxanes) or single-agent IO (if

accessible). Enrollment in clinical trials is highly encouraged, recognizing that trials in this setting require global recruitment.

Novel or Emerging Therapeutic Options

For patients who have progressed on the abovementioned lines of therapy, contemporary clinical research has explored several novel treatment combinations including epigenetic agents, vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibition, bispecific immunotherapies, and novel anti-PD-1 agents.[24-30] In this setting, ORRs of 10-30%, PFS of 4-6 months, and OS of 12-18 months have been achieved in small prospective phase II studies.

For example, the phase II open-label, non-randomized, multicentre basket trial PEVOsq assessed pembrolizumab and vorinostat, a histone deacetylase (HDAC) inhibitor, in a mixed cohort of recurrent or metastatic SCC, including 29 patients with mASCC.[25] The combination therapy resulted in an ORR of 31%, with a mOS of 18.8 and mPFS of 5.8 months.[25] Further, a phase II trial of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) in 20 previously IO treatment-naïve patients revealed an ORR of 10%, PFS of 4.1 months (95% CI, 2.6 - NA), and mOS of 11.6 months (95% CI, 9.5-20).[26] Other early-phase drug trials in this space have evaluated avelumab (anti-PD-L1), avelumab plus cetuximab (anti-EGFR), atezolizumab plus bevacizumab, bintrafusp alfa (PD-L1 and TGF-β blocking bispecific fusion protein), and other PD-L1 inhibitor combinations with ORRs ranging from 11%-31%.[26-30]

EGFR-targeted therapies have also been trialed due to similarities to cervical and head and neck tumours in terms of histology, radiosensitivity of early-stage disease, and biologically HPV-associated disease.[30] These cancers (cervical and head and neck) likewise overexpress EGFR, and in a cohort of 101 patients 90% were positive for EGFR by IHC. Further, EGFR-targeted treatment resistance mechanisms involving downstream effector (*KRAS* and *BRAF*) mutations are less common than in other cancers.[30] Based on this, anti-EGFR treatment with cetuximab was assessed in a series of heavily pretreated patients in combination with irinotecan. A response was observed in 5 of 7 patients, with a median PFS of 6 months. Although promising, this treatment has not yet been investigated in a larger phase II trial.[30]

Conclusions

While recent advances in systemic treatment options have improved outcomes for patients with advanced or metastatic ASCC, treatment in this context represents an as-of-yet unmet need in the management of solid tumours. The addition of IO to a chemotherapy backbone in the phase III POD1UM-303/InterAAct-2 trial has established retifanlimab and carboplatin plus paclitaxel as the standard of care for advanced or metastatic ASCC with improved PFS and OS (although survival results remain immature). For ICI-ineligible patients, the InterAAct trial established carboplatin plus paclitaxel as another standard of care. In the second-line setting, options include single-agent IO, chemotherapy, and clinical trials, depending on prior lines of treatment, patient performance status, and underlying comorbidities. Current biology-informed studies are examining combination regimens that include HDAC inhibitors, EGFR-targeted therapies, and VEGF-targeted therapies. Ongoing global efforts are necessary to advance the science and management of this challenging disease.

Correspondence

Michael Vickers, MD, MPH, FRCPC
Email: mvickers@toh.ca

Financial Disclosures

V.D.: None declared.
D.B.: None declared.
M.V.: None declared.

References

1. Canadian Cancer Society. Anal cancer statistics [Internet]. Toronto (ON): Canadian Cancer Society; 2025 Nov [cited 2026 Jan 29]. Available from: https://cancer.ca/en/cancer-information/cancer-types/anal/statistics
2. Racine M, Meurette G, Ris F, Meyer J, Toso C, Liot E. Management of squamous cell carcinomas of the anal canal and anal margin after failure of chemoradiotherapy treatment: a narrative review. Cancers (Basel). 2025;17(9):1511. doi:10.3390/cancers17091511.
3. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal—the spectrum of disease, treatment, and outcomes. Cancer. 1999;85(8):1686–1693. doi:10.1002/(SICI)1097-0142(19990415)85:8<1686::AID-CNCR7>3.0.CO;2-7.
4. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). SEER

Explorer: An interactive website for SEER cancer statistics* [Internet]. National Cancer Institute, DCCPS, SRP; [cited 2026 Jan 29]. Available from: https://seer.cancer.gov/statistics-network/explorer/application.html?site=34&data_type=1&graph_type=2&compareBy=sex&chk_sex_2=2&chk_sex_3=3&rate_type=2&race=1&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on#resultsRegion0

5. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol. 2014;40(10):1165-76. doi: 10.1016/j.ejso.2014.07.030.
6. Dhawan N, Afzal MZ, Amin M. Immunotherapy in anal cancer. Curr Oncol. 2023;30(5):4538–4550. doi:10.3390/curroncol30050343.
7. Ajani JA, Carrasco CH, Jackson DE, Wallace S. Combination of cisplatin plus fluoropyrimidine chemotherapy effective against liver metastases from carcinoma of the anal canal. Am J Med. 1989;87(2):221–224. doi:10.1016/S0002-9343(89)80702-8.
8. Faivre C, Rougier P, Ducreux M, Mitry E, Lusinchi A, Lasser P, et al. 5-Fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer. 1999;86(10):861–865.
9. Kim S, Jary M, Mansi L, Benzidane B, Cazorla A, Demarchi M, et al. DCF (docetaxel, cisplatin and 5-fluorouracil) chemotherapy is a promising treatment for recurrent advanced squamous cell anal carcinoma. Ann Oncol. 2013;24(12):3045–3050. doi:10.1093/annonc/mdt396.
10. Hainsworth JD, Burris HA 3rd, Meluch AA, Baker MN, Morrissey LH, Greco FA. Paclitaxel, carboplatin, and long-term continuous infusion of 5-fluorouracil in the treatment of advanced squamous and other selected carcinomas: Results of a Phase II trial. Cancer. 2001;92(3):642–649. doi:10.1002/1097-0142(20010801)92:3<642::AID-CNCR1365>3.0.CO;2-Z.
11. Jaiyesimi IA, Pazdur R. Cisplatin and 5-fluorouracil as salvage therapy for recurrent metastatic squamous cell carcinoma of the anal canal. Am J Clin Oncol. 1993;16(5):536540. doi:10.1097/00000421-199312000-00017.
12. Rao S, Sclafani F, Eng C, Adams RA, Guren MG, Sebag-Montefiore D, et al. International Rare Cancers Initiative multicenter randomized phase II trial of cisplatin and fluorouracil versus carboplatin and paclitaxel in advanced anal cancer (InterAAct). J Clin Oncol. 2020;38(22):2510–2518. doi:10.1200/JCO.19.03266.
13. Morel A, Neuzillet C, Wack M, Lameiras S, Vacher S, Deloger M, et al. Mechanistic signatures of human papillomavirus insertions in anal squamous cell carcinomas. Cancers (Basel). 2019;11:1846. doi:10.3390/cancers11121846.
14. Ciardiello D, Guerrera LP, Maiorano BA, Parente P, Latiano TP, Di Maio M, et al. Immunotherapy in advanced anal cancer: Is the beginning of a new era? Cancer Treat Rev. 2022;105:102373. doi:10.1016/j.ctrv.2022.102373.
15. Rao S, Samalin Scalzi E, Evesque L, Ben Abdelghani M, Morano F, Roy A, et al. Retifanlimab with carboplatin and paclitaxel for locally recurrent or metastatic squamous cell carcinoma of the anal canal (POD1UM 303/InterAACT 2): a global, phase 3 randomised controlled trial. Lancet. 2025;405(10495):2144–2152. doi:10.1016/S0140 6736(25)00631 2.
16. Kim S, Byer J, Fulp WJ, Mahipal A, Dinwoodie W, Shibata D. Carboplatin and paclitaxel treatment is effective in advanced anal cancer. Oncology. 2014;87(2):125-132.
17. Pignata S, Scambia G, Katsaros D, Gallo C, Pujade-Lauraine E, De Placido S, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised phase 3 trial. Lancet Oncol. 2014;15(4):396-405. doi:10.1016/S1470-2045(14)70049-X.
18. National Cancer Institute (NCI). EA2176: Phase 3 clinical trial of carboplatin and paclitaxel +/- nivolumab in metastatic anal cancer patients. ClinicalTrials.gov [Internet]. 2026 Jan 29 [cited 2026 Jan 29]; Available from: https://clinicaltrials.gov/ct2/show/NCT04444921
19. Centre Hospitalier Universitaire de Besancon. SPARTANA: Combination of spartalizumab, mDCF and radiotherapy in patients with metastatic squamous cell carcinoma. ClinicalTrials.gov [Internet]. 2023 Dec 22 [cited 2026 Jan 29]; Available from: https://clinicaltrials.gov/ct2/show/NCT04894370
20. Upadhyay L, Hartzell M, Parikh AR, Strickland MR, Klempner S, Malla M. Recent advances in the management of anal cancer. Healthcare (Basel). 2023;11(23):3010. doi:10.3390/healthcare11233010.
21. Rao S, Anandappa G, Capdevila J, Dahan L, Evesque L, Kim S, et al. A phase II study of retifanlimab (INCMGA00012) in patients with squamous carcinoma of the anal canal who have progressed following platinum-based chemotherapy (POD1UM-202). ESMOOpen. 2022;7(4):100529. doi:10.1016/j.esmoop.2022.100529.
22. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord J-P, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38(1):1-10. doi:10.1200/JCO.19.02105.
23. Morris VK, Salem ME, Nimeiri H, Iqbal S, Singh P, Ciombor K, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18(4):446-453. doi:10.1016/S1470-2045(17)30104-3.
24. Morris VK, Ciombor KK, Xiao L, Ochieng JK, Marmonti E, Polite B, et al. NCI9673 (Part B): ETCTN randomized phase II study of nivolumab with or without ipilimumab in refractory, metastatic squamous cell carcinoma of the anal canal. J Clin Oncol. 2026;44(6):497-507. doi:10.1200/JCO-25-00929.
25. Borcoman E, Cabarrou B, Francisco M, Bigot F, Ghiringhelli F, Vansteene D, et al. Efficacy of pembrolizumab and vorinostat combination in patients with recurrent and/or metastatic squamous cell carcinomas: a phase 2 basket trial. Nat Cancer.

2025;6(8):1370-1383. doi:10.1038/s43018-025-01004-2.
26. Morris VK, Liu S, Lin K, Zhu H, Prasad S, Mahvash A, et al. Phase II trial of atezolizumab and bevacizumab for treatment of HPV-positive unresectable or metastatic squamous cell carcinoma of the anal canal. Clin Cancer Res. 2025;31(9):1657-1666. doi:10.1158/1078-0432.CCR-24-1512.
27. Rao S, Capdevila J, Gilbert D, Kim S, Dahan L, Kayyal T, et al. International Rare Cancers Initiative multicenter randomized phase II trial of cisplatin and fluorouracil versus carboplatin and paclitaxel in advanced anal cancer: InterAAct. J Clin Oncol. 2020;38(22):2510-2518. doi:10.1200/JCO.19.03266.
28. Lonardi S, Prete AA, Morano F, Messina M, Formica V, Corsi DC, et al. Randomized phase II trial of avelumab alone or in combination with cetuximab for patients with previously treated, locally advanced, or metastatic squamous cell anal carcinoma: the CARACAS study. J Immunother Cancer. 2021;9(11). doi:10.1136/jitc-2021-002996.
29. Strauss J, Gatti-Mays ME, Cho BC, Hill A, Salas S, McClay E, et al. Bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in patients with human papillomavirus-associated malignancies, including anal squamous cell carcinoma. J Immunother Cancer. 2020;8(2):e001395. doi:10.1136/jitc-2020-001395
30. Saif MW, Kontny E, Syrigos KN, Shahrokni A. The role of EGFR inhibitors in the treatment of metastatic anal canal carcinoma: a case series. J Oncol. 2011;2011:125467. doi:10.1155/2011/125467.

doi.org/10.58931/cot.2026.3145

About the Author

Zineb Hamilou, MD

Dr. Zineb Hamilou is a hematologist and medical oncologist trained at the University of Montreal. She is an assistant professor at the University of Montreal and an investigator at the CHUM Research Centre. She completed postdoctoral training in genitourinary cancers with a particular interest in prostate cancer. Within the oncology and uro-oncology research team, she participates in the care of patients enrolled in multiple phase I, II, III research protocols.

Affiliations: Department of Medicine, Hematology-Oncology Division, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC

Metastatic CRPC: Contemporary Therapeutic Options and Optimal Sequencing

Zineb Hamilou, MD

Introduction

Prostate cancer (PC) is the most common malignancy among men worldwide. In Canada, an estimated 27,900 new diagnoses were projected in 2024, accounting for approximately 22% of all new cancer cases, with nearly 5,000 related deaths, making PC the fifth leading cause of cancer mortality.[1] Approximately 8% of patients present with metastatic disease at diagnosis.[2] Moreover, rates of *de novo* metastatic PC have increased in recent years, likely reflecting both the widespread adoption of advanced imaging modalities and reduced systematic screening practices.[2,3]

Initial treatment for recurrent or *de novo* metastatic castration-sensitive prostate cancer (mCSPC) typically consists of androgen-deprivation therapy (ADT) combined with an androgen receptor pathway inhibitor (ARPI). In patients with high-volume disease, which is defined as ≥4 bone metastases (including ≥1 outside the vertebral column) or the presence of visceral metastases, triplet therapy with ADT, an ARPI, and docetaxel chemotherapy may be employed.[4-6] In contrast, biochemical recurrence without radiographic metastases is generally managed with ADT alone, with treatment intensification using enzalutamide for patients with a prostate-specific antigen (PSA) doubling time between 3 and 9 months, as supported by the EMBARK trial.[7]

Despite initial disease control, most patients ultimately progress while maintaining castrate testosterone levels, a state known as castration-resistant prostate cancer (CRPC), which may be metastatic (mCRPC) or non-metastatic (nmCRPC). Over 84% of patients are estimated to have metastatic disease at the time of CRPC diagnosis.[8]

This review summarizes the current and evolving treatment landscape for mCRPC and proposes an evidence-based approach to treatment sequencing in accordance with the 2025 Canadian Urological Association Canadian Uro-Oncology Group guidelines and the National Comprehensive Cancer Network (NCCN) recommendations.[9,10]

General Principles for Treatment Selection

Metastatic CRPC is defined by disease progression despite ongoing ADT and castrate serum testosterone levels (<50 ng/dL or <1.7 nmol/L). Persistent androgen receptor signaling remains a key driver of disease progression, partly due to intratumoural autocrine and paracrine androgen synthesis.[11] Consequently, ADT is maintained indefinitely in patients with mCRPC.

Biochemical progression is defined as a PSA rise of ≥2 ng/mL or ≥50% above nadir, confirmed by three consecutive measurements at least one week apart.[12] Radiographic progression is assessed according to Prostate Cancer Working Group 3 (PCWG3) criteria.[13]

For patients who developed mCRPC, biopsy of metastatic lesions is recommended when feasible, along with molecular testing for homologous recombination repair (HRR) gene mutations (particularly *BRCA*1/2) and microsatellite instability (MSI)/mismatch repair (MMR) deficiency.[9,10] HRR testing may be performed on archival primary tumour tissue, fresh metastatic biopsy, or circulating tumour DNA when tissue is unavailable or non-informative.

Given the increasing use of ARPIs and chemotherapy in earlier disease states, treatment sequencing in mCRPC has become increasingly complex and must account for prior therapies, response duration, toxicity, and patient comorbidities.

Androgen Receptor Pathway Inhibitors

Abiraterone acetate plus prednisone (AAP) was the first ARPI to demonstrate survival benefit in mCRPC. In a phase III trial involving post-chemotherapy patients, AAP significantly improved progression-free survival (PFS) and overall survival (OS) compared with placebo.[14] Subsequently, the COU-AA-302 trial showed that AAP significantly prolonged median PFS in patients with chemotherapy-naïve mCRPC (16.5 vs. 8.3 months; hazard ratio [HR]: 0.53, 95% confidence interval [CI]: 0.45–0.62), leading to its approval in this setting.[15]

Enzalutamide, a second-generation ARPI, also demonstrated OS and PFS benefits in mCRPC after chemotherapy in the AFFIRM trial.[16] In the PREVAIL trial, enzalutamide significantly improved OS in patients with chemotherapy-naïve mCRPC, with a median OS of 35.2 versus 31.0 months (HR: 0.71, 95% CI: 0.60–0.84).[17,18]

In nmCRPC, enzalutamide, apalutamide, and darolutamide have all demonstrated clinically meaningful improvements in metastasis-free survival and OS when added to continuous ADT in patients with high-risk disease (PSA doubling time ≤10 months), forming the standard of care in this setting.[19-21]

For patients presenting with *de novo* mCRPC who have previously received ADT alone, first-line treatment typically consists of an ARPI (AAP or enzalutamide), either alone or in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor in the presence of HRR mutations.

Taxane Chemotherapy

Taxane chemotherapy remains a cornerstone of mCRPC treatment. Docetaxel demonstrated a median OS improvement of approximately 3 months over mitoxantrone in the TAX 327 trial and is most commonly used as first-line chemotherapy.[22]

Cabazitaxel, a next-generation taxane developed to overcome docetaxel resistance, has demonstrated efficacy across multiple trials. In the TROPIC trial, cabazitaxel improved OS compared with mitoxantrone in post-docetaxel patients (15.1 vs. 12.7 months; HR: 0.70, 95% CI: 0.59–0.83).[23] The PROSELICA trial established non-inferiority of the 20 mg/m² dose compared with 25 mg/m², with improved tolerability.[24] Importantly, the CARD trial showed that cabazitaxel was superior to switching to an alternative ARPI in patients previously treated with docetaxel and one ARPI, improving both radiographic PFS (8.0 vs. 3.7 months; HR: 0.54, 95% CI: 0.40–0.73) and OS (13.6 vs.11.0 months; HR: 0.64, 95% CI: 0.46–0.89).[25]

Targeted Therapies

HRR Gene Mutations and PARP Inhibitors

Up to 30% of patients with metastatic PC harbour germline or somatic DNA repair gene alterations, most commonly involving *BRCA2* or *BRCA1*.[26-29] These mutations are associated with poorer prognosis but confer sensitivity to PARP inhibition.

In the post-ARPI setting, the PROfound trial demonstrated that olaparib significantly improved radiographic PFS (7.4 vs. 3.6 months; HR: 0.34, 95% CI: 0.25–0.47) and OS (18.5 vs. 15.1 months;

HR: 0.69, 95% CI: 0.50–0.97) compared with switching to another ARPI in patients with *BRCA1/2* or *ATM* alterations, despite crossover.[30]

First-line combinations of PARP inhibitors with ARPIs have also shown benefit in first-line treatment of mCRPC. The PROpel trial demonstrated improved radiographic PFS with olaparib plus abiraterone compared with abiraterone alone (24.8 vs. 16.6 months; HR: 0.66; 95% CI: 0.54 to 0.81), with the greatest benefit observed in HRR-mutated tumours.[31] This combination is approved by Health Canada for *BRCA1/2*-mutated mCRPC.

Similarly, the MAGNITUDE trial showed improved PFS with niraparib plus AAP in HRR-mutated mCRPC.[32] Recently, the TALAPRO-2 trial demonstrated that talazoparib plus enzalutamide improved both PFS and OS compared with enzalutamide alone, irrespective of HRR status. This treatment resulted in radiographic mPFS of 33.1 vs. 19.5 months (HR: 0.667, 95% CI: 0.551–0.807) and an OS of 45.8 vs. 37.0 months (HR: 0.796, 95% CI: 0.661–0.958).[33] The benefit was most pronounced in HRR-mutated tumours, where the combination produced a deeper and more durable radiographic PFS advantage compared with HRR-non-mutated disease.

PSMA-Targeted Radioligand Therapy

Patients with mCRPC progressing after ARPI and taxane chemotherapy may be eligible for PSMA-targeted radioligand therapy (RLT), contingent upon PSMA positron emission tomography (PET) imaging demonstrating PSMA-positive disease without discordant PSMA-negative lesions.

In the phase III VISION trial, beta-emitter lutetium-177-PSMA-617 plus standard of care significantly improved radiographic PFS (8.7 vs. 3.4 months; HR: 0.40, 99.2% CI: 0.29–0.57) and OS (15.3 vs. 11.3 months; HR: 0.62, 95% CI: 0.52–0.74) compared with standard care alone.[34] Although higher rates of grade ≥3 adverse events were observed, quality of life was preserved.

In taxane-naïve mCRPC, the PSMAfore and SPLASH trials demonstrated significant improvements in radiographic PFS compared with ARPI switching, though no OS benefit was observed, likely due to crossover.[35,36]

Immunotherapy

MMR deficiency, MSI-high status, or high tumour mutational burden (TMB) are identified in a minority of patients with mCRPC (1.2–12.0%) and may predict benefit from immune checkpoint inhibition.[28] Pembrolizumab has tumour-agnostic approval for these patients, with retrospective data demonstrating meaningful PSA and radiographic responses.[28,37] However, phase III trials of pembrolizumab combinations in unselected mCRPC populations have not demonstrated survival benefit.[38-40]

Other Therapies

Alpha-emitter Radium-223 dichloride (^{223}Ra) demonstrated improved OS and delayed skeletal-related events in the ALSYMPCA trial for patients with symptomatic bone-only mCRPC.[41] ^{223}Ra is an option for patients with mCRPC with symptomatic bone metastases and/or lymph nodes ≤3 cm in the absence of visceral disease.

Mitoxantrone, an anthracenedione antineoplastic agent, provides palliative benefit without OS improvement and is now rarely used.[42,43] The cellular therapy sipuleucel-T improved OS in asymptomatic mCRPC in the IMPACT trial but is not approved by Health Canada.[44]

Supportive Therapy

Bone metastases occur in approximately 90% of patients with mCRPC and these patients are thus subject to skeletal-related events.[45-47] These include pathological fractures, debilitating bone pain requiring palliative radiation therapy, and spinal cord compression, all of which may significantly affect quality of life.

Zoledronic acid and denosumab reduce skeletal-related events, with denosumab demonstrating superiority over zoledronic acid in delaying time to first event.[46,47] Bone-modifying agents should be routinely considered, with appropriate dental evaluation to mitigate the risk of osteonecrosis of the jaw.

Treatment Sequencing

Treatment sequencing in mCRPC is largely driven by prior systemic therapy exposure and should be individualized based on clinical and biological characteristics, as well as patient comorbidities.

Approximately 20–50% of patients treated with curative intent ultimately develop biochemical recurrence and progress to mCRPC, most often after prior exposure to ADT and an ARPI. Upon development of castration resistance, these patients typically transition to docetaxel chemotherapy while continuing ADT.

Similarly, patients presenting with (mCSPC) are now frequently treated upfront with ADT in combination with an ARPI, with the addition of docetaxel in those with high-volume disease. At progression to mCRPC, docetaxel is initiated, if not previously administered, or may be reintroduced in selected patients who achieved a durable prior response.

In contrast, for patients harbouring a pathogenic *BRCA1* or *BRCA2* mutation who experience progression following ARPI therapy, treatment with a PARP inhibitor, most notably olaparib, is recommended in lieu of immediate taxane chemotherapy.

As discussed earlier, lutetium-177-PSMA-617 may be considered in patients with prior exposure to an ARPI and at least one line of chemotherapy.

Finally, cabazitaxel and ^{223}Ra represent established therapeutic options that can be incorporated into the treatment sequence based on disease characteristics, prior therapies, symptom burden, and patient fitness.

Conclusion

Therapeutic advances have substantially improved outcomes for patients with mCRPC, offering prolonged survival and improved quality of life. Nonetheless, the disease remains incurable, and optimal sequencing of increasingly complex treatment options requires careful consideration of prior therapies and molecular features. Participation in clinical trials remains essential to further advance care for this population.

Correspondence

Zineb Hamilou, MD
Email: zineb.hamilou.med@ssss.gouv.qc.ca

Financial Disclosures

Z.H.: Honorarium for consultations and conferences: AstraZeneca, EMD Serono/Pfizer, Astellas, Merck, Novartis; **Honorarium for conferences:** Canadian Urology Association, Association des médecins hématologues et oncologues du Québec, Fédération des médecins spécialistes du Québec; **Research Grant:** AstraZeneca

References

1. Brenner DR, Gillis J, Demers AA, Ellison LF, Billette JM, Zhang SX, et al. Projected estimates of cancer in Canada in 2024. CMAJ. 2024;196(18):E615-23. https://doi.org/10.1503/cmaj.240095
2. Canadian Cancer Society. Cancer statistics [Internet]. Toronto (ON): Canadian Cancer Society; [cited 2026 Jan 7]. Available from: https://cancer.ca/en/research/cancer-statistics
3. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA Cancer J Clin. 2025;75(1):10-45. https://doi.org/10.3322/caac.21871
4. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373(8):737-46. https://doi.org/10.1056/nejmoa1503747
5. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med. 2022;386(12):1132-42. https://doi.org/10.1056/nejmoa2119115
6. Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R, Flechon A, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet. 2022;399(10336):1695-707. https://doi.org/10.1016/S0140-6736(22)00367-1
7. Freedland SJ, de Almeida Luz M, De Giorgi U, Gleave M, Gotto GT, Pieczonka CM, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med. 2023;389(16):1453-65. https://doi.org/10.1056/NEJMoa2303974
8. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011;65(11):1180-92. https://doi.org/10.1111/J.1742-1241.2011.02799.X
9. Saad F, So AI, Aprikian A, Finelli A, Fleshner NE, Gleave ME, et al. 2025 Canadian Urological Association-Canadian Uro-oncology Group Guideline: Metastatic castration-resistant prostate cancer (Update). Can Urol Assoc J. 2025;19(8):E276-E89. https://doi.org/10.5489/cuaj.9341
10. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.4.2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed December 12th 2025.
11. Cai C, Balk SP. Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. Endocr Relat Cancer. 2011;18(5):R175-82. https://doi.org/10.1530/ERC-10-0339
12. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol. 2017;71(4):630-42. https://doi.org/10.1016/j.eururo.2016.08.002
13. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: updated

recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18. https://doi.org/10.1200/JCO.2015.64.2702
14. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005. https://doi.org/10.1056/NEJMoa1014618
15. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-48. https://doi.org/10.1056/NEJMoa1209096
16. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97. https://doi.org/0.1056/NEJMoa1207506
17. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424-33. https://doi.org/10.1056/NEJMoa1405095
18. Armstrong AJ, Lin P, Tombal B, Saad F, Higano CS, Joshua AM, et al. Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer from the PREVAIL trial. Eur Urol. 2020;78(3):347-57. https://doi.org/10.1016/j.eururo.2020.04.061
19. Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2020;382(23):2197-206. https://doi.org/10.1056/NEJMoa2003892
20. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378(15):1408-18. https://doi.org/10.1056/NEJMoa1715546
21. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2019;380(13):1235-46. https://doi.org/10.1056/NEJMoa1815671
22. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12. https://doi.org/10.1056/NEJMOA040720
23. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54. https://doi.org/10.1016/S0140-6736(10)61389-X
24. Eisenberger M, Hardy-Bessard AC, Kim CS, Geczi L, Ford D, Mourey L, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m(2)) and the currently approved dose (25 mg/m(2)) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. J Clin Oncol. 2017;35(28):3198-206. https://doi.org/10.1200/JCO.2016.72.1076
25. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wulfing C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med. 2019;381(26):2506-18. https://doi.org/10.1056/NEJMoa1911206
26. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375(5):443-53. https://doi.org/10.1056/NEJMoa1603144
27. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215-28. https://doi.org/10.1016/j.cell.2015.05.001
28. Abida W, Armenia J, Gopalan A, Brennan R, Walsh M, Barron D, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol. 2017;2017. https://doi.org/10.1200/PO.17.00029
29. Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Vargas HA, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol. 2019;5(4):471-8. https://doi.org/10.1001/JAMAONCOL.2018.5801
30. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382(22):2091-102. https://doi.org/10.1056/NEJMoa1911440
31. Saad F, Clarke NW, Oya M, Shore N, Procopio G, Guedes JD, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24(10):1094-108. https://doi.org/10.1016/S1470-2045(23)00382-0
32. Chi KN, Sandhu S, Smith MR, Attard G, Saad M, Olmos D, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. Ann Oncol. 2023;34(9):772-82. https://doi.org/10.1016/j.annonc.2023.06.009
33. Agarwal N, Azad AA, Carles J, Fay AP, Matsubara N, Heinrich D, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023;402(10398):291-303. https://doi.org/10.1016/S0140-6736(23)01055-3
34. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021;385(12):1091-103. https://doi.org/10.1056/NEJMOA2107322
35. Morris MJ, Castellano D, Herrmann K, de Bono JS, Shore ND, Chi KN, et al. (177)Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer

(PSMAfore): a phase 3, randomised, controlled trial. Lancet. 2024;404(10459):1227-39. https://doi.org/10.1016/S0140-6736(24)01653-2
36. Sartor O, Jiang DM, Smoragiewicz M, Zibelman M, Flechon A, El-Haddad G, et al. Efficacy of ^{177}Lu-PNT2002 in PSMA-positive mCRPC following progression on an androgen-receptor pathway inhibitor (SPLASH). Presented at: European Society for Medical Oncology (ESMO) Congress 2024; 13-17 September 2024; Barcelona, Spain. Abstract LBA65.
37. Graham LS, Montgomery B, Cheng HH, Yu EY, Nelson PS, Pritchard C, et al. Mismatch repair deficiency in metastatic prostate cancer: Response to PD-1 blockade and standard therapies. PLoS One. 2020;15(5):e0233260. https://doi.org/10.1371/JOURNAL.PONE.0233260
38. Graff JN, Burotto M, Fong PC, Pook DW, Zurawski B, Manneh Kopp R, et al. Pembrolizumab plus enzalutamide versus placebo plus enzalutamide for chemotherapy-naive metastatic castration-resistant prostate cancer: the randomized, double-blind, phase III KEYNOTE-641 study. Ann Oncol. 2025;36(8):976-87. https://doi.org/10.1016/j.annonc.2025.05.007
39. Petrylak DP, Ratta R, Matsubara N, Korbenfeld E, Gafanov R, Mourey L, et al. Pembrolizumab plus docetaxel versus docetaxel for previously treated metastatic castration-resistant prostate cancer: the randomized, double-blind, phase III KEYNOTE-921 trial. J Clin Oncol. 2025;43(14):1638-49. https://doi.org/10.1200/JCO-24-01283
40. Antonarakis ES, Park SH, Goh JC, Shin SJ, Lee JL, Mehra N, et al. Pembrolizumab plus olaparib for patients with previously treated and biomarker-unselected metastatic castration-resistant prostate cancer: the randomized, open-label, phase III KEYLYNK-010 trial. J Clin Oncol. 2023;41(22):3839-50. https://doi.org/10.1200/JCO.23.00233
41. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23. https://doi.org/10.1056/NEJMoa1213755
42. Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. J Urol. 2002;168(6):2439-43. https://doi.org/10.1016/S0022-5347(05)64163-8
43. Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol. 1996;14(6):1756-64. https://doi.org/10.1200/JCO.1996.14.6.1756
44. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-22. https://doi.org/10.1056/NEJMoa1001294
45. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96(11):879-82. https://doi.org/10.1093/jnci/djh141
46. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009;361(8):745-55. https://doi.org/10.1056/NEJMoa0809003
47. Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813-22. https://doi.org/10.1016/S0140-6736(10)62344-6

About the Authors

Giulia Pool, MD

Giulia Pool, MD, is a medical oncologist and Assistant Professor at the University of Sherbrooke. She completed her medical and oncology training at the University of Sherbrooke and a fellowship in gastrointestinal oncology at the University of British Columbia under Howard Lim. Her clinical practice and research both focus on gastrointestinal cancers and treatment-related toxicities with contribution to colorectal cancer studies and presentations at major conferences including American Society of Clinical Oncology.

Affiliations: BC Cancer, Vancouver Centre, Vancouver, BC, Canada

Janine M. Davies, MD, BN, MSc, FRCPC

Dr. Davies is a medical oncologist at BC Cancer, Vancouver and Clinical Assistant Professor in the Division of Medical Oncology at the University of British Columbia. Dr. Davies earned her Bachelor of Nursing degree (with distinction) and Master of Science in Health Research at the University of Calgary. She earned her MD from McMaster University and completed her residency in Internal Medicine and Medical Oncology at the University of Calgary. She then completed a 2-year fellowship in Gastrointestinal (GI) Oncology and Drug Development at the University of North Carolina at Chapel Hill and worked on faculty as an Assistant Professor. She joined BC Cancer, Kelowna in 2011 then Vancouver in 2015. Her research interests are primarily in the areas of GI oncology, advanced care planning and survivorship, improving access to care and treatment, physician well-being, and team capacity building, and coaching on quality improvement projects.

Affiliations: BC Cancer, Vancouver Centre, Vancouver, BC, Canada
University of British Columbia, Department of Medicine, Vancouver, BC, Canada

doi.org/10.58931/cot.2026.3146

Second-line Treatment Strategies in Biliary Tract Cancers

Giulia Pool, MD
Janine M. Davies, MD, BN, MSc, FRCPC

Introduction

Biliary tract cancers (BTCs) are a highly heterogenous group of tumours arising from the bile ducts (cholangiocarcinoma [CCA]) and gallbladder. Of note, tumours of the ampulla of Vater typically fall under this definition but tend to be excluded from second-line treatment studies. Cholangiocarcinomas are further classified into intrahepatic (iCCA, including hilar) and extrahepatic (eCCA). Together, they account for approximately 15% of primary liver cancers and 3% of all gastrointestinal malignancies.[1] However, iCCA and eCCA are separate entities that differ in incidence, clinical presentation, natural evolution, and molecular profile. Specifically, iCCA is less commonly associated with biliary obstructive symptoms and thus tends to be diagnosed incidentally and at a more advanced stage than eCCA.[2] The diagnostic challenges partly stem from the localization of these tumours, deep in the hepatic and biliary systems, where it is often difficult to obtain a tissue biopsy or an adequate aspiration cytology. iCCA can be misclassified as carcinoma of unknown primary (CUP) as histologically it can be impossible to distinguish from metastatic adenocarcinoma of an extrahepatic primary tumour, and the primary tumour can be small and not well identified on imaging.

The unique features of these tumours may in part explain their poor prognosis. Overall, the 5-year survival rate of CCA is estimated to be less than 25% for all stages combined, reflecting a very modest treatment effect.[1] Chemoimmunotherapy combinations are now globally accepted as the standard first-line treatment, but uncertainties remain regarding second and later lines of treatment. This review will summarize the available treatments beyond the first line with a focus on the emerging field of molecular precision medicine.

First-line Standard of Care

The ABC-02 trial has established the chemotherapy standard of care for first-line treatment of locally advanced or metastatic BTCs. The gemcitabine and cisplatin (GC) combination (8 cycles) showed a significant survival advantage compared to gemcitabine alone (6 cycles) with a median progression-free survival (PFS) of 8.0 months vs. 5.0 months ($p < 0.001$), and a median overall survival (OS) of 11.7 months vs. 8.1 months ($p < 0.001$).[3]

More recently, two trials have confirmed the added benefit of immunotherapy to this chemotherapy backbone. The TOPAZ-01 trial confirmed the superiority of the addition of durvalumab (programmed cell death ligand 1 [PD-L1] inhibitor) to GC with a median OS of 12.9 months (95% confidence interval [CI]: 11.6–14.1) vs. 11.3 months (95% CI: 10.1-12.5) in the placebo and GC groups, respectively (hazard ratio [HR]: 0.76, 95% CI: 0.64-0.91).[4] The KEYNOTE-966 trial yielded similar results with the combination of pembrolizumab (programmed cell death protein 1 [PD-1] inhibitor) and GC with a median OS of 12.7 months (95% CI: 11.5–13.6) vs. 10.9 months (95% CI: 9.9–11.6) in the placebo and GC group, respectively (HR: 0.83, 95% CI: 0.72–0.95).[5] To date, no biomarkers have been confirmed for patient selection.

Therefore, in the absence of contraindication to immunotherapy, the addition of either durvalumab or pembrolizumab to GC represents the new standard of care for patients with previously untreated metastatic or unresectable BTCs.

Second-line Therapy and Beyond

Chemotherapy for Unselected Groups

Until 2019, the role of second-line chemotherapy after progression on GC was unclear with retrospective studies suggesting a benefit only in patients with a good performance status. Some retrospective series and systematic reviews suggested that around 30-40% of patients would be fit enough for this treatment.[6] However, it has been estimated that only 15-25% of patients went on to receive second-line therapy.[7]

Although the advent of molecular precision medicine has led to the development of new targeted therapies, more than half of CCAs do not express any actionable mutations. For those patients, second-line treatment comprises chemotherapy either as a combination or single agent. Several different chemotherapy agents have been used based on phase II or retrospective trials, including fluoropyrimidine, irinotecan, docetaxel, gemcitabine, and platinum-based compounds.[7-13]

Folinic Acid, Fluorouracil, and Oxaliplatin (FOLFOX)

The pivotal ABC-06 trial was the first prospective, adequately powered, randomized trial showing a survival benefit for FOLFOX compared to active symptom control alone (median OS: 6.2 months vs. 5.3 months). At 12 months, the OS rate was more than doubled with chemotherapy (25.9% vs. 11.4%).[7] Results of quality of life (QoL) analyses presented at the European Society for Medical Oncology (ESMO) congress in 2022 showed that FOLFOX allowed stabilized QoL and helped avoid worsening nausea and pain.[8] This regimen is considered the standard of care second-line option for unselected patients in the absence of a targeted therapy with better outcomes. Notably, the benefit of single agent fluoropyrimidine compared to doublet therapy remains unknown.

Folinic Acid, Fluorouracil, and Irinotecan (FOLFIRI)

The NIFTY trial was a promising phase II study evaluating nano-liposomal irinotecan (nal-IRI) and 5-fluorouracil (5-FU) compared to 5-FU alone after progression on GC. Conducted exclusively in South Korea, the study showed a median PFS of 4.2 months for the combination vs. 1.7 months with 5-FU alone. The 6-month PFS rates were 31.8% vs.15.1%, respectively.[9] A second phase II study conducted in Korea failed to demonstrate superiority of modified formulations of FOLFIRI to FOLFOX (mFOLFIRI to mFOLFOX) with 6-month OS of 44.1% vs. 54.1%, respectively. Both regimens, however, appeared to have similar antitumour activity in terms of objective response rate (ORR) and disease control rate (DCR) (4.0% and 64.0%, respectively, with mFOLFIRI vs. 5.9% and 66.7% with mFOLFOX).[10] In the absence of confirmatory studies in a Western population, FOLFIRI is considered as a reasonable alternative option to FOLFOX, for example if oxaliplatin is contraindicated.[11]

Capecitabine/5-FU

The benefit of a fluoropyrimidine-platinum combination therapy compared to fluoropyrimidine alone has been inconsistent between studies. A 2017 retrospective study of 748 patients from Korea showed that the combination was associated with higher response rates than monotherapy (8% vs. 1%) after failure of GC, but this did not translate into significant improvements in PFS (median 2.6 vs. 1.8 months) or OS (median 6.2 vs 6.5 months).[12] Another retrospective study of 325 patients treated at BC Cancer from 2009 to 2015 also seemed to support the use of single-agent capecitabine following failure of first-line treatment. Notably, the included cohort was obtained prior to the ABC-06 trial: capecitabine was the most used regimen (30%), followed by FOLFIRI (17%), and 5-FU monotherapy (15%). The median OS was prolonged for all patients who received second-line chemotherapy as compared to patients who only received first-line chemotherapy (17.3 months vs. 9.5 months), regardless of the second-line regimen used.[13]

No randomized trials have been conducted to assess the value of systemic treatment in advanced CCA without an actionable mutation beyond second line.[6]

Precision Medicine and Targeted Therapies

Research in molecular profiling techniques and precision medicine has led to a better understanding of the driving mechanisms behind the oncogenesis of BTCs. Through DNA next-generation sequencing (NGS) and RNA sequencing (RNAseq), multiple tumour gene alterations have been identified in this cancer type, for which targeted therapies may be available. It is estimated

that up to 40% of CCA have actionable targets with different frequencies in iCCA, eCCA, and gallbladder carcinoma (GBC).[14] Of the alterations with data supporting the use of targeted drugs, the most frequent are rearrangements and fusions of the fibroblast growth factor receptor 2 (*FGFR2*) in iCCA, mutations of the genes encoding isocitrate dehydrogenases 1 and 2 (*IDH1, IDH2*) in iCCA, amplification and/or overexpression of the *ERBB2* gene encoding the protein HER2 (in GBC > eCCA > iCCA) **(see Figure 1)**. Other alterations, such as the presence of microsatellite instability (GBC), *BRAF* V600E mutation (GBC), *KRAS* G12C, and *NTRK* fusion are less frequent. **Table 1** summarizes the current available options for each that will be discussed in this article.

FGFR

FGFR2 fusions or rearrangements are observed in 10-20% of CCAs, almost exclusively in iCCA. First-generation FGFR inhibitors are non-selective tyrosine kinase inhibitors. Their broad effects on multiple receptor tyrosine kinases (RTKs) are thus accompanied by a challenging toxicity profile, which has led to the development of second-generation pan-FGFR inhibitors.[16] The main second-generation molecules and their respective phase II trials are summarized in **Table 2**.

One of the largest trials with pemigatinib included patients with unresectable or metastatic CCA (predominantly iCCA) having received at least one previous treatment. Patients were pre-screened centrally for *FGF/FGFR* status using DNA sequencing (including patients with a previous *FGF/FGFR* status report based on local assessment) and assigned to one of three cohorts: (A) *FGFR2* fusions or rearrangements, (B) other *FGF/FGFR* alterations, or (C) no *FGF/FGFR* alterations. Of 1,206 patients that were pre-screened (and 85 included from a previous report), 146 patients were enrolled, the vast majority in cohort A (107 patients). In this cohort, 35.5% achieved an objective response (three complete responses and 35 partial responses; 95% CI: 26.5-45.4) with a DCR of 82%. Although not mature at the data cut-off, median PFS was 6.9 months (95% CI: 6.2-9.6) and median OS 21.1 months (95% CI:

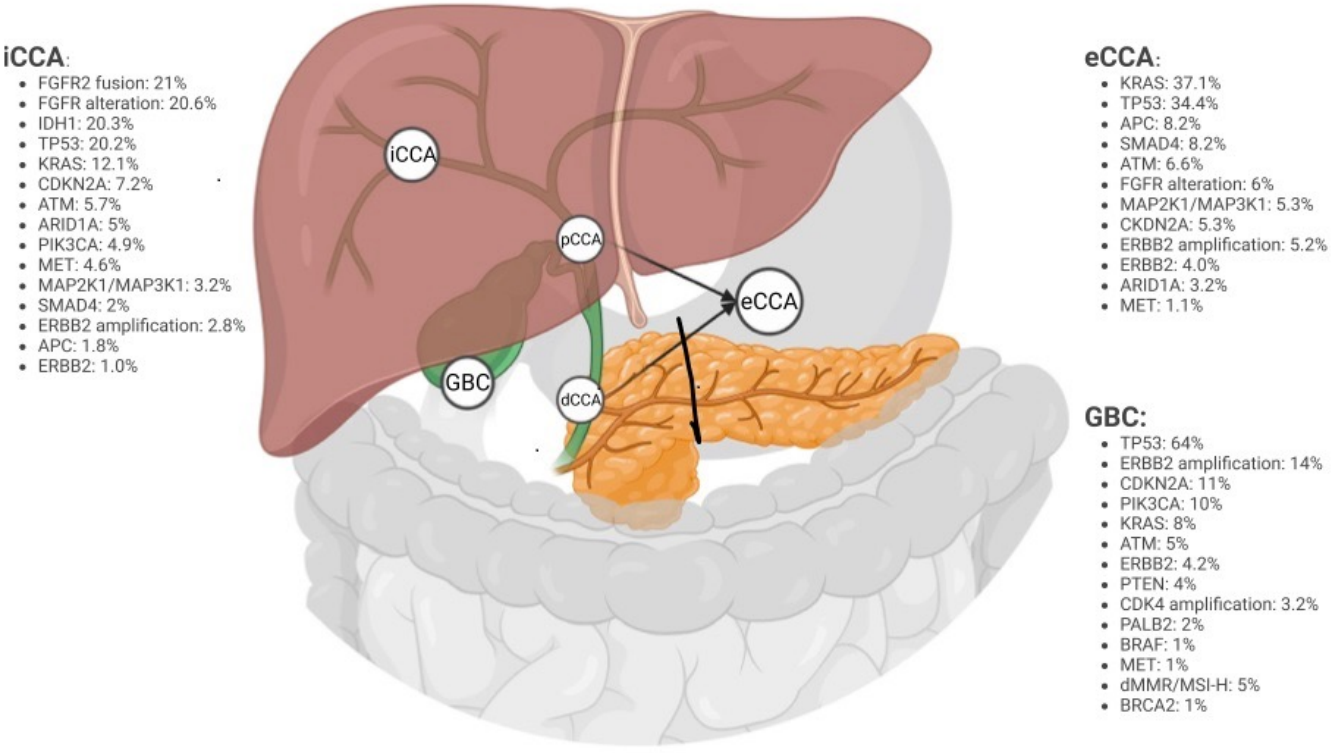

Figure 1. Biliary tract cancer molecular alteration prevalence by subtype[15]; *courtesy of Giulia Pool, MD, and Janine M. Davies, MD, BN, MSc, FRCPC.*

Abbreviations: 1L: eCCA: extrahepatic cholangiocarcinoma; **GBC:** gallbladder carcinoma; **iCCA:** intrahepatic cholangiocarcinoma.

Target	Molecule
FGFR	Pemigatinib Infigratinib Derazantinib
IDH1	Ivosidenib
Her2	Trastuzumab, pertuzumab Zanidatamab Neratinib
NTRK	Larotrectinih Entrectinib
BRAF	Dabrafenib, trametinib

Table 1. Precision oncology options for biliary tracts cancers; *courtesy of Giulia Pool, MD, and Janine M. Davies, MD, BN, MSc, FRCPC.*

14.8- not estimable [NE]).[17] The results for cohort B and cohort C were less promising but included a very small number of patients (20 and 18 patients, respectively). Trials of infigratinib and derazantinib are less mature but show lower response rates and similar mPFS.[18]

The adverse events associated with these agents are similar as a class, and overall, well tolerated. They include hyperphosphatemia, stomatitis, diarrhea, hand-foot syndrome, and fatigue. Hyperphosphatemia can, however, be quite serious, requiring serial serum phosphate monitoring, low-phosphorus dietary modifications, phosphate binders or phosphaturic agents, and sometimes dose reductions. Retinopathy is another serious potential complication, most associated with erdafitinib.[16]

Together, these promising results have led to several ongoing trials assessing FGFR inhibitors in the first-line setting. Another active focus of research is understanding the resistance mechanisms to these agents, both for the primary refractory patients and those with acquired resistance. For example, in a phase I study of the third-generation FGFR inhibitor futibatinib, approximately one third of patients had previously received FGFR inhibitors, mostly ATP-competitive inhibitors such as pemigatinib. Of these patients, 17.9% still experienced objective responses[20], suggesting a potential benefit of sequential treatment strategies in FGFR2-altered CCAs beyond the second line.

IDH1/2

Somatic point mutations in *IDH1* and *IDH2* genes have been associated with the production and accumulation of the onco-metabolite D2-hydroxyglutarate (D-2HG) that leads to epigenetic changes, impaired DNA repair, and aberrant cell metabolism, promoting tumourigenesis. *IDH1* mutations are detected in approximately 15-20%

	Trial	Phase and study design	Population (treatment line)	Primary objectives	Results		
					ORR	mPFS	mOS
Pemigatinib	FIGHT-202[17]	Single-arm multicentre phase II	n = 147 (L2+)	ORR	Cohort fusion: 35.5%	6.9 months	21.1 months
Infigratinib	CBGJ398X2204[18]	Single-arm multicentre phase II	n = 61 (L2+)	ORR	14.8%	5.8 months	N/A
Derazantinib	FIDES-01[19]	Single-arm multicentre phase II	n = 28 (L2+)	mPFS	Best overall response 8.7%	7.3 months	N/A

Table 2. Published studies evaluating targeted therapies against *FGFR* fusions; *courtesy of Giulia Pool, MD, and Janine M. Davies, MD, BN, MSc, FRCPC.*

Abbreviations: mOS: median overall survival; **mPFS:** median progression-free survival; **N/A:** not available; **ORR:** objective response rate.

of iCCA, compared to 0.8% of eCCA. Only one *IDH-1* inhibitor, ivosidenib, has been tested in a phase III trial for patients with *IDH1*-mutated CCA who progressed on up to two previous treatment regimens for advanced disease. Of the 230 patients screened, 187 were randomized (2:1) to receive either ivosidenib or placebo. More than 90% of the patients had iCCA and approximately 55% had received only one prior line of therapy. The PFS was significantly improved with ivosidenib (4 months) compared with placebo (2.7 months). The benefit in median OS was not statistically significant, possibly due to a high rate of crossover between the two groups. The treatment appeared to be well tolerated, the most common treatment-related adverse events being nausea (35%), diarrhea (31%), and fatigue (26%).[21] Many other IDH-mutant inhibitors and IDH pathway target therapies are currently under investigation in clinical trials.

HER2

Alterations of the *ERRB2* or HER2/Neu gene include amplifications, overexpression, or more rarely mutations. HER2 amplification is more prevalent in eCCA and gallbladder cancer (5%-15%) but is also observed in iCCA. Although no phase III trials have been published for this subset of patients, there is an undeniable interest in developing new strategies in HER2-amplified CCA.

The MyPathway phase IIa multiple basket study is an ongoing trial investigating pertuzumab plus trastuzumab in patients with HER2-positive advanced biliary tract cancer after at least one previous line of treatment. Patients were enrolled based on HER2-positive archival or fresh tumour tissue samples. At the March 10, 2020 cut-off, 661 patients were enrolled, including 39 patients with a HER2-positive BTC (90% had HER2 amplification without overexpression or overexpression status unknown). The ORR for this treatment regimen was 23%, the DCR 51%, median PFS was 4.0 months, and median OS was 10.9 months.[22] While the results are preliminary, they support a potential new application for these anti-HER2 therapies already included in guidelines for other cancer types with HER2 positivity.

New agents are also being investigated, such as zanidatamab, a bispecific antibody targeting two distinct HER2 epitopes. The HERIZON-BTC-01 phase IIb trial yielded promising results with zanidatamab monotherapy (ORR: 41.3%, DCR: 68.8%, median PFS: 5 months) for patients who progressed on previous gemcitabine-based therapy. The trial is ongoing but now closed to recruitment. The toxicity profile also appeared to be acceptable with the most common adverse events being diarrhea (32%), infusion-related reactions (32%), and decreased ejection fraction (6%).[23]

Targeting gene mutations rather than gene amplification may also have potential. The SUMMIT trial is an open-label, single-arm, multi-cohort, phase II, 'basket' trial investigating neratinib in patients with solid tumours harbouring oncogenic HER2 somatic mutations. In the BTC cohort, 25 treatment refractory patients were enrolled. The results were positive, although modest (ORR: 16%, median PFS: 2.8 months, OS: 5.4 months) reflecting the need to conduct further studies looking at combinations to improve the responses. However, the study has been terminated based on the sponsor's development plans for neratinib (and not based on any new efficacy or safety data for neratinib).[24]

Neurotrophic Tyrosine Receptor Kinase (NTRK)

Fusions of one of the three *NTRK* genes (1, 2, or 3) are rare alterations in BTCs (<1%). However, small trials with NTRK inhibitors have shown high response rates and durable responses. Larotrectinib is a potent and highly selective small-molecule inhibitor of all three TRK proteins. A phase I/II trial of *TRK* fusion–positive cancers, with only 2 of 55 patients enrolled having CCA, reported an ORR of 75% with a 1-year PFS of 55% for all patients. Only one patient with CCA had a tumour response.[25]

Entrectinib is another NTRK1, 2, 3 inhibitor that has shown promising results. An integrated database comprising of datasets of three ongoing phase I or III clinical trials reported the results in a population of 54 adults with advanced or metastatic *NTRK* fusion-positive tumours (only 1 CCA). Nevertheless, that patient was among the responders, with an ORR of 57% and median PFS of 11.2 months.[26]

Both therapies appear to be safe with most treatment-related adverse events being grade 1-2 and reversible, such as increased alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) levels, fatigue, nausea/ vomiting, diarrhea, dizziness, and anemia.

BRAF

The *BRAF* gene encodes a serin/threonine protein kinase activating the MAP kinase/ERK

signaling pathway. Activating mutations have been described mainly in iCCA with a prevalence of 1-3%. The V600E mutation of the *BRAF* gene is particularly of interest because it is potentially targetable with dual inhibition of BRAF and MEK. The phase II ROAR basket trial investigated the combination of dabrafenib and trametinib in 8 cohorts of patients, including 43 patients with BTCs. The ORR was ≥50% across all cohorts (except high-grade gliomas). The median PFS was 9 months in the BTC cohort and OS was 13.5 months. The most reported adverse events were pyrexia (54.9%), fatigue (42.2%), and nausea (41.7%).[27]

KRAS

Although an activating mutation of the *KRAS* oncogene is found in 15-25% of BTC, only the KRASG12C mutation is accessible to pharmacological inhibition, which is present in 1% of CCAs. KRYSTAL-1 is a multicohort phase I/II study evaluating the KRASG12C selective and irreversible inhibitor adagrasib in patients with previously treated advanced solid tumours harbouring that mutation. A total of 42 patients were enrolled in this cohort, including 8 patients with BTCs. In a preliminary analysis, the reported ORR was 50% with a DCR of 100%. The most frequent adverse events were nausea (48%), diarrhea (43%), vomiting (43%) and fatigue (29%).[28] Although these treatments are not yet approved, inclusion of patients in clinical trials assessing adagrasib or sotorasib (another oral inhibitor specific for KRASG12C) is encouraged based on these results.

DNA Mismatch Repair Deficiency (dMMR) and/or Microsatellite Instability-high (MSI-H) Tumours

Beyond the first line combinations, immunotherapy has also been studied in BTCs, notably for patients with dMMR and/or MSI-H tumours, which account for 1-3% of all CCAs. The phase II KEYNOTE-158 trial enrolled 233 patients with previously treated advanced cancers from 27 non-colorectal tumour types, including 22 patients (9.4%) with MSI-H/dMMR CCAs with either somatic or germline MSI mutations. Of note, prior anti-PD-1 and anti-PD-L1 treatment were exclusion criteria for this study. Among CCAs, the ORR was 40.9%, PFS was 4.2 months, and OS was 24.3 months.[29]

In comparison, the role of immunotherapy in previously treated microsatellite stable (MSS)/proficient mismatch repair (pMMR) BTCs, especially after first-line immunotherapy, remains unclear. To date, trials have shown very modest benefits in this population of both single and dual agent immunotherapy.[10]

Other Immunotherapy Combinations with Kinase Inhibitors

Because of the disappointing results of immunotherapy alone in pMMR tumours, several trials have suggested a potential benefit of combining targeted small-molecule therapeutics with immune checkpoint inhibitors (ICIs) to increase their efficacy and produce more durable responses. One proposed strategy is to combine ICIs with anti-angiogenic therapies. The addition of the anti-angiogenic agent is thought to improve immunotherapy activity by contributing to lymphocyte cytotoxicity in the tumour microenvironment. The LEAP-005 trial evaluated the efficacy and safety of lenvatinib and pembrolizumab in patients with previously treated advanced solid tumours, including a BTC cohort of 31 patients. The results for that subgroup included an ORR of 10%, median PFS of 6.1 months, and median OS of 8.6 months.[30] Several trials investigating similar combinations of immunotherapy and anti-angiogenic therapies are ongoing. This could offer another option for previously treated advanced BTC without actionable mutations and help avoid chemotherapy-related toxicity.

Challenges in Molecular Testing

Despite the clear benefit of personalized medicine and molecular profiling, the clinical application of this strategy comes with several new challenges. One of the main issues is related to tissue sampling. Molecular profiling should be performed as early as possible, ideally at the initial diagnosis stage and early in treatment, to prevent later treatment delays. In some cases, sample testing may need to be repeated due to insufficient diagnostic tissue quality or quantity. This is especially true for iCCA, which is located deep in the hepatic and biliary system and difficult to access. Even for early stages of disease, it is important to consider preservation of tissue and sparing enough material to allow complimentary molecular analyses if recurrence occurs in the future. BTCs are aggressive tumours and patients tend to decline too rapidly to be eligible to start a second-line therapy, so any delay in testing

and delivering the results can thus have major consequences.[6]

Another challenge is related to the nature of each gene alteration and the specific testing that they might require. For example, NGS is used to detect mutations of genes such as *IDH1*, *BRAF*, and *KRAS*. The fusions or rearrangements of genes such as *FGFR2* or *NTRK* require RNAseq, which might not be included in all NGS panels. Although most NGS panels search for amplification/overexpression of *ERBB2* by studying the copy number variant of the gene, overexpression of HER2 protein is observed by immunohistochemistry (IHC) and requires confirmation by fluorescent *in situ* hybridization (FISH) when IHC overexpression is 2+.[31] MSI can be identified using DNA sequencing panels or through IHC staining of mismatch repair system (MMR) proteins to detect MMR deficiency.[6]

Another significant obstacle is the access and funding for these tests. Currently, there is no funded platform for molecular testing for patients in Canada. However, the Canadian Cholangiocarcinoma Collaborative (C3) works to facilitate patients' access to testing and identifying potential clinical trial opportunities.

ctDNA

Liquid biopsies refer to blood sampling meant to detect circulating tumour DNA (ctDNA), circulating cell-free RNA (ccfRNA), and cell-free DNA (cfDNA). This approach has gained popularity in cancer trials over the last decade for its diagnostic potential, and since it allows for molecular target selection, response monitoring, and resistance tracking.

A study evaluating the concordance between intrapatient ctDNA and tumour tissue mutations among 102 patients with BTC showed a sensitivity of 84.8% and positive predictive value of 79.4%. ctDNA analysis could identify targetable alterations in 34.3% of patients, including *FGFR2* fusions, *IDH1* mutations, MSI-H, and *ERBB2* amplifications.[32] In BTCs specifically, liquid biopsies may eventually provide an alternative to the challenging tissue-based analysis previously discussed.

A trial with futibatinib used genomic characterization of pre- and post-progression ctDNA to better understand patterns of resistance, ultimately showing that futibatinib was active against multiple *FGFR2* mutations that conferred resistance to earlier generations FGFR inhibitors.[33] ctDNA not only represents a useful tool at the time of diagnosis, but dynamic monitoring may also help predict the effect of therapy and identify the emergence of acquired resistance mutations during treatment. This may in turn help clinicians make treatment adjustments in a timely manner and provide a rationale for eventual sequential treatment strategies.[34]

Liquid biopsy has already proven effective in many other malignancies, but data on the application of ctDNA for BTC remains immature. Liquid biopsy can be considered for disease molecular profiling, but further research is warranted for its use in response monitoring and resistance tracking to ultimately optimize treatment strategies.

Conclusion

Cholangiocarcinomas are rare malignancies with an increasing incidence, especially for iCCA. Despite significant improvements associated with chemoimmunotherapy combinations in the advanced first-line setting, the prognosis remains extremely poor. The advent of personalized medicine has changed the treatment paradigm for many patients with advanced BTCs. As molecular profiling represents a new standard of care, it should be obtained early to tailor each patient's treatment. However, this remains a significant challenge in terms of access to both the molecular tests and the corresponding targeted agents. Because of the rarity of CCAs, most clinical trials include a small number of patients and are typically prospective/retrospective nonrandomized single-arm studies. More research is needed to optimize biomarker identification, patient selection, and the use of combination therapies to optimize treatment strategies.

Correspondence

Janine Davies, MD, FRCPC
Email: janine.davies@bccancer.bc.ca

Financial Disclosures

G.P.: None Declared.
J.D.: Honoraria: Astra-Zeneca; **Ad boards**: Eisai, Taiho, Amgen, Astellas

References

1. Wang Y, Li Y, Liang Z, Zhang Y, Li T, Tian C, et al. Circulating tumor DNA in cholangiocarcinoma: current clinical applications and future perspectives. Front Cell Dev Biol. 2025;13:1616064.
2. Bekaii-Saab TS, Valle JW, Van Cutsem E, Rimassa L, Furuse J, Ioka T, et al. FIGHT-302: first-line pemigatinib vs gemcitabine plus cisplatin for advanced cholangiocarcinoma with FGFR2 rearrangements. Future Oncol. 2020;16(30):2385-99.
3. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273-81.
4. 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.
5. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. 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):1853-65.
6. Roth GS, Neuzillet C, Sarabi M, Edeline J, Malka D, Lievre A. Cholangiocarcinoma: what are the options in all comers and how has the advent of molecular profiling opened the way to personalised medicine? Eur J Cancer. 2023;179:1-14.
7. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. 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;22(5):690-701.
8. Lamarca A, Palmer D, Wasan HS, Ross P, Ma YT, Arora A, et al. 54MO Quality of life (QoL) and value of health (V-He) in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+FOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial. Annals of Oncology. 2022;33:S564-S5.
9. Hyung J, Kim I, Kim KP, Ryoo BY, Jeong JH, Kang MJ, et al. Treatment with liposomal irinotecan plus fluorouracil and leucovorin for patients with previously treated metastatic biliary tract cancer: the phase 2b NIFTY randomized clinical trial. JAMA Oncol. 2023;9(5):692-9.
10. Elvevi A, Laffusa A, Scaravaglio M, Rossi RE, Longarini R, Stagno AM, et al. Clinical treatment of cholangiocarcinoma: an updated comprehensive review. Ann Hepatol. 2022;27(5):100737.
11. Lamarca A, Edeline J, Goyal L. How I treat biliary tract cancer. ESMO Open. 2022;7(1):100378.
12. Kim BJ, Yoo C, Kim KP, Hyung J, Park SJ, Ryoo BY, et al. Efficacy of fluoropyrimidine-based chemotherapy in patients with advanced biliary tract cancer after failure of gemcitabine plus cisplatin: retrospective analysis of 321 patients. Br J Cancer. 2017;116(5):561-7.
13. Mathers B, Abadi S, Davies JM, McIntyre C, Ho C. Use, response and outcomes of second-line chemotherapy in patients with advanced biliary tract cancers. J Oncol Pharm Pract. 2023;29(6):1381-6.
14. Vienot A, Neuzillet C. Cholangiocarcinoma: the quest for a second-line systemic treatment. Transl Cancer Res. 2019;8(Suppl 3):S275-S88.
15. Wheless M, Agarwal R, Goff L, Lockney N, Padmanabhan C, Heumann T. Current standards, multidisciplinary approaches, and future directions in the management of extrahepatic cholangiocarcinoma. Curr Treat Options Oncol. 2024;25(1):127-60.
16. Chen L. Next-generation isoform-selective fibroblast growth factor receptor inhibitors. Trends Pharmacol Sci. 2025;46(11):1091-104.
17. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21(5):671-84.
18. Javle M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. J Clin Oncol. 2018;36(3):276-82.
19. Javle MM, Abou-Alfa GK, Macarulla T, Personeni N, Adeva J, Bergamo F, et al. Efficacy of derazantinib in intrahepatic cholangiocarcinoma patients with FGFR2 mutations or amplifications: Interim results from the phase 2 study FIDES-01. J Clin Oncol. 2022;40(4_suppl):427.
20. Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau HT, et al. Futibatinib, an irreversible FGFR1-4 inhibitor, in patients with advanced solid tumors harboring FGF/FGFR aberrations: a phase I dose-expansion study. Cancer Discov. 2022;12(2):402-15.
21. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. 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.
22. Javle M, Borad MJ, Azad NS, Kurzrock R, Abou-Alfa GK, George B, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2021;22(9):1290-300.
23. Harding JJ, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, et al. 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(7):772-82.
24. Harding JJ, Piha-Paul SA, Shah RH, Cleary JM, Quinn DI, Brana I, et al. Targeting HER2 mutation–positive advanced biliary tract cancers with neratinib: Final results from the phase 2 SUMMIT basket trial. J Clin Oncol. 2022;40:Suppl 16; abstr 4079.
25. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731-9.
26. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet

Oncol. 2020;21(2):271-82.
27. Subbiah V, Kreitman RJ, Wainberg ZA, Gazzah A, Lassen U, Stein A, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. Nat Med. 2023;29(5):1103-12.
28. Bekaii-Saab TSS, Spira AII, Yaeger R, Buchschacher Jr. GLL, McRee AJJ, Sabari JKK, et al. KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRASG12C mutation. J Clin Oncol. 2022; 40: suppl. 4:abstr 519.
29. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38(1):1-10.
30. Villanueva L, Lwin Z, Chung HCC, Gomez-Roca CA, Longo F, Yanez E, et al. Lenvatinib plus pembrolizumab for patients with previously treated biliary tract cancers in the multicohort phase 2 LEAP-005 study. Journal of Clinical Oncology. 2021;39(15_suppl):4080.
31. Ten Haaft BH, Pedregal M, Prato J, Klumpen HJ, Moreno V, Lamarca A. Revolutionizing anti-HER2 therapies for extrahepatic cholangiocarcinoma and gallbladder cancer: Current advancements and future perspectives. Eur J Cancer. 2024;199:113564.
32. Hwang S, Woo S, Kang B, Kang H, Kim JS, Lee SH, et al. Concordance of ctDNA and tissue genomic profiling in advanced biliary tract cancer. J Hepatol. 2025;82(4):649-57.
33. Goyal L, Shi L, Liu LY, Fece de la Cruz F, Lennerz JK, Raghavan S, et al. TAS-120 overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma. Cancer Discov. 2019;9(8):1064-79.
34. de Scordilli M, Bortolot M, Torresan S, Noto C, Rota S, Di Nardo P, et al. Precision oncology in biliary tract cancer: the emerging role of liquid biopsy. ESMO Open. 2025;10(5):105079.

About the Authors

Safiya Karim, MD, MSc, FRCPC

Safiya Karim is a Medical Oncologist and Clinical Associate Professor at the Arthur J.E Child Comprehensive Cancer Centre and the University of Calgary. Her clinical practice is in gastrointestinal and genitourinary cancers. Her research interests include real-world evidence and outcomes, quality improvement, and global oncology. Nationally, she is the chair of the Choosing Wisely Oncology working group. She also serves as the director of the Medical Oncology Fellowship Program and Assistant Director of the Oncology Outcomes (02) program. She has published more than 50 peer-reviewed manuscripts in high quality journals including *Journal of Clinical Oncology*, *JAMA Oncology*, and *Nature Reviews Clinical Oncology*.

Affiliations: Department of Oncology, Arthur J.E. Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB

Claire Browne, MD

Dr. Claire Browne is currently completing her fellowship at the University of Calgary in Integrative Oncology and Palliative Care. She earned her MD degree from Western University, where she also completed her residencies in Internal Medicine and Medical Oncology.

Affiliations: Department of Oncology, Arthur J.E. Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB

Linda E. Carlson, Ph.D, R.Pysch, FCAHS, FABMR

Dr. Linda Carlson holds the Enbridge Research Chair in Psychosocial Oncology and is a Full Professor in the Department of Oncology, Cumming School of Medicine at the University of Calgary. She directs the Alberta Complementary Therapy and Integrative Oncology (ACTION) Centre and has provided clinical care at Cancer Care Alberta since 1997. A globally recognized leader in mindfulness-based cancer recovery and integrative oncology, Dr. Carlson has published over 280 peer-reviewed works, co-authored influential books, and received numerous prestigious awards, including the 2023 Dr. Rogers Prize in Complementary and Alternative Medicine. She also serves as Co-Editor-in-Chief of the *Journal of Psychosocial Oncology Research and Practice*, is Past-President of the Society for Integrative Oncology and Treasurer for the International Society for Contemplative Research.

Affiliations: Department of Oncology, Arthur J.E. Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB

doi.org/10.58931/cot.2026.3147

Integrative Medicine and Cancer: 5 Ways to Incorporate Integrative Oncology into Routine Clinical Practice

Safiya Karim, MD, MSc, FRCPC
Claire Browne, MD
Linda E. Carlson Ph.D, R.Pysch, FCAHS, FABMR

Key Messages

- Integrative oncology is patient-centred, evidence-informed field of comprehensive cancer care that utilizes mind-body practices, natural products and lifestyle modifications alongside conventional cancer treatment.
- The Society of Integrative Oncology (SIO) and the American Society of Clinical Oncology (ASCO) have produced four evidence-based clinical practice guidelines for integrative therapies in oncology care.
- Practioners may consider non-pharmacologic evidence-based integrative therapies for a variety of cancer and treated related symptoms.
- Encouraging patients to eat a high-quality diet and to be active before, during, and after cancer treatment is beneficial.
- Establishing trust with patients who use dietary supplements is important in developing a therapeutic relationship.

Introduction

In 2018, over 1.5 million people in Canada were living with or after a cancer diagnosis.[1] While survival from cancer has increased steadily since the 1990s due to advances in screening, diagnosis, and more effective treatments, symptoms of cancer or side effects from treatment continue to affect the physical, emotional, and spiritual well-being of individuals.[2] While some people may turn to alternative therapies, many individuals seek an integrated approach to care (one that uses evidence-informed complementary therapies together with conventional medicine) **(Box 1)**.

Over the past 50 years, there has been substantial growth in the number of people with cancer using complementary therapies, from 20% in 1970 to 80% in 2017.[3]

To meet this need, many National Cancer Institute (NCI)- designated comprehensive cancer centres in the United States and centres in other countries have developed integrative oncology programs that offer evidence-informed, personalized, integrative cancer care.[4] Integrative Oncology, as defined by the Society for Integrative Oncology (SIO), is a “patient-centred, evidence-informed field of comprehensive cancer care that utilizes mind-body practices, natural products and lifestyle modifications alongside conventional cancer treatment".[5]

However, public Canadian comprehensive and community cancer centres have yet to implement integrative oncology programs into routine care. In the absence of structured programs, we suggest five ways oncologists can incorporate integrative oncology concepts into routine clinical practice to better support the needs of people with cancer.

Alternative Therapies are interventions that are chosen instead of conventional cancer care. They are not usually evidence-based and often are very expensive or require travel to other countries to access. They are not part of integrative oncology care.
Complementary Therapies are interventions, products, and procedures that are not traditionally part of conventional medical care but are typically used alongside conventional cancer treatments.

Integrative Oncology is a patient-centred, evidence-informed field of comprehensive cancer care that utilizes mind and body practices, natural products and lifestyle modifications alongside conventional cancer treatments.

1. Familiarize Yourself With the SIO/American Society of Clinical Oncology (ASCO) Guidelines

In 2020, ASCO and the SIO announced they would collaborate on producing a series of evidence-based clinical practice guidelines for integrative therapies in oncology care. To date, four guidelines have been published: Management of Fatigue in Adult Survivors of Cancer,[6] Cannabis and Cannabinoids in Adults with Cancer,[7] Integrative Oncology Care for Anxiety and Depression in Adults with Cancer,[8] and Integrative Medicine for Pain Management in Oncology.[9] The development of these guidelines indicates the commitment to the promotion of safe and effective use of integrative approaches in cancer care. Clinicians should familiarize themselves with these guidelines to provide an evidence-based approach to complementary therapies. In addition, oncology providers are encouraged to take continuing education modules on pain management and anxiety and depression guidelines.[10]

2. Include Evidence-based Non-pharmacological Recommendations for Symptom Management

Certain symptoms and side effects of cancer treatment may respond well to integrative therapies. In addition, people living with cancer may prefer these therapies over pharmacological treatments as they are perceived as less likely to interact with other treatments or cause additional side effects, and are often approaches they can learn and apply on their own.

Anxiety and/or Depression

Psychological distress, including anxiety and depression, is associated with poor quality of life and higher mortality in individuals with cancer. The strongest recommendation from the joint SIO/ASCO guideline is that mindfulness-based interventions (MBIs) should be offered during and after cancer treatment (quality of evidence: high; strength of Evidence: strong).[8] MBIs include mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), and mindfulness-based cancer recovery (MBCR), which is specifically designed for people with cancer. Other recommendations for management of anxiety and depression during or after cancer treatment include yoga, music therapy, relaxation therapies, reflexology, and tai chi/qi gong.[8] Many of these modalities may be offered through psychosocial oncology or survivorship programs at public cancer centres, community cancer partners (i.e., Wellspring), general community programs for the public, or private psychotherapists.

Pain

For people with cancer, pain can be a result of tumour burden on associated structures and organs and/or may be due to side effects of treatments, including surgery, chemotherapy, immunotherapy, hormonal therapy, and radiation. Pain management requires an interdisciplinary approach and may include both pharmacologic and nonpharmacologic treatments. In the 2022 joint SIO/ASCO guideline on integrative medicine for pain management in oncology, several nonpharmacologic treatments are recommended based on an intermediate level of evidence and a moderate strength of recommendation.[9] For aromatase inhibitor-induced joint pain, acupuncture may be considered based on the results of several systematic reviews and randomized controlled trials, including a large phase III randomized trial.[11] Acupuncture and/or reflexology may be beneficial for people who have general or musculoskeletal pain from cancer, and hypnosis may benefit those who have procedural pain. Massage therapy may also be used, especially for patients in palliative or hospice care.[9]

Fatigue

Cancer-related fatigue (CRF) is a persistent, often overwhelming feeling of physical, mental, and/or emotional exhaustion that differs from fatigue caused by exertion, as it is not necessarily relieved by rest or sleep.[6] Up to 60% of people with cancer experience moderate-to-severe fatigue during cancer treatment, and up to 30% continue to experience fatigue months or even years after treatment completion.[12] During treatment, the incorporation of exercise, cognitive behavioural therapy (CBT), and mindfulness-based programs can improve CRF. In addition, during treatment, tai chi, qi gong, and American ginseng can be considered. After treatment completion,

yoga, acupressure, and moxibustion have been shown to be beneficial.[6]

Other symptoms that may respond well to integrative therapies include vasomotor disturbances,[13,16] insomnia,[14,16] chemotherapy-induced nausea and vomiting,[15,16] and radiation-induced dry mouth.[17]

3. Encourage People with Cancer to be Active Before, During, and After Cancer Treatment

Physical activity is important for people with cancer before, during, and after cancer treatment. A combination of aerobic and anaerobic physical activity has been shown to improve several outcomes, including fatigue, quality of life, anxiety and depression, physical fitness, risk of recurrence, and mortality.[18] In a recently published randomized controlled trial, a 3-year structured exercise program initiated soon after completion of adjuvant chemotherapy improved disease-free and overall survival in people with a history of colorectal cancer.[19] This was a significant finding as the magnitude of the effect of regular exercise on survival was similar to many anti-cancer drugs, with fewer adverse effects. Several guidelines recommend 150 min of moderate-intensity aerobic exercise, 3–5 sessions per week, and resistance training at least 2 days per week, as part of a 6–12 week program.[20] Physical activity recommendations should be individualized and tailored based on disease type and severity, comorbidities, and baseline physical fitness. Exercise sessions should be supervised, at least at the outset, by a certified trainer or physical therapist.

4. Discuss the Benefits of a High-quality Diet During and AfterTreatment

Diet plays an important role in maintaining health throughout a person's cancer journey. A high-quality diet includes high proportions of vegetables, fruits, beans/legumes, protein, and whole grains with limited proportions of foods with added sugar, high sodium, refined grains, and processed meats.[21] Such diets have been shown to reduce mortality,[21,22] improve health-related quality of life,[22] and reduce CRF.[23-26] Conversely, low protein intake may be associated with increased mortality and increased CRF.[23] Dietary patterns showing benefit on cancer-specific and overall survival in people with breast cancer include the Mediterranean diet, the dietary approaches to stop hypertension (DASH) diet, and adherence to the Chinese Food Pagoda.[21,22] These diets encourage high intake of fibre, fruit and vegetables, whole grains, and fish, while limiting intake of sodium, red and processed meats, and saturated fat. In patients with breast cancer undergoing adjuvant chemotherapy, a plant-based, high-protein diet improved fatigue, body mass index, and body composition.[25] Furthermore, in women with breast cancer who had completed treatment, a 3-month diet rich in fruit, vegetables, whole grains, and omega-3-fatty acids (named the fatigue reduction diet), improved fatigue and sleep compared to a general health curriculum.[24] While most of the dietary cancer research has been performed in women with breast cancer, some of the benefits are likely applicable to people with other malignancies.

The American Institute for Cancer Research (AICR) has developed evidence-based dietary recommendations for cancer prevention.[27] These emphasize eating plant-based foods, including whole grains, fruits, vegetables, and beans, while limiting consumption of alcohol, red and processed meats, and sugar. These recommendations can also be followed during and after cancer treatment. However, as these recommendations do not always consider ethnic preferences for specific foods, a dietitian may be beneficial in developing individualized meal plans.

5. Establish Trust With Patients Who May Take Dietary Supplements

Up to 80% of people with cancer use some form of dietary supplements, with 14-32% of patients starting a dietary supplement after a cancer diagnosis.[28] However, a significant proportion of patients do not discuss their supplement use with a healthcare provider, with common reasons including not being asked, expectation of disapproval, or perceived provider disinterest in the topic. In addition, oncologists report discussing supplement use with only a minority of their patients, with patients most commonly initiating the discussion.[29]

A significant concern with dietary supplements is the potential for interaction with medications, including anti-cancer drugs. In one study, 18% of patients were taking a supplement

that had potentially harmful interactions with their cancer therapies.[30] An integrative oncology clinic in the US reported that 35% of patients received at least one recommendation to discontinue a particular supplement following a detailed medication review.[31] However, such interactions can only be discovered if supplement use is discussed.

Oncologists should inquire what supplements their patients are using; these discussions significantly increase patient satisfaction with care.[29] Unfortunately, most studies regarding supplement use in the oncology setting are limited to observational studies or small phase I/II trials, so the quality of evidence regarding their efficacy is limited. If available, people undergoing cancer treatment should be directed to other integrative therapies that have shown benefit for a particular symptom or side effect before recommending dietary supplements. If a patient is committed to taking a dietary supplement, careful consideration must be given to its quality, safety, and potential drug interactions. Various databases can be referenced, including EfficaSafe,[32] AboutHerbs,[33] and the NatMed database.[34] Many integrative oncology programs have also incorporated clinical pharmacists to assist with supplement-related counselling,[35] and pharmacist involvement in the care of patients utilizing multiple supplements should be encouraged.

Conclusion

Integrative Oncology incorporates evidence-based integrative therapies into cancer care using a patient-centred approach. Clinicians should be aware of the evidence supporting these therapies and be comfortable discussing these data with patients. In the end, an integrated approach to care can maintain trust and rapport and improve the quality of life in people with cancer.

Correspondence

Safiya Karim, MD, MSc, FRCPC
Email: Safiya.Karim@albertahealthservices.ca

Financial Disclosures

S.K.: None declared.
C.B.: None declared.
L.C.: None declared.

References

1. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2025. Toronto (ON): *Canadian Cancer Society; 2025*. Available from: https://cancer.ca/Canadian-Cancer-Statistics-2025-EN. Accessed 2026 Jan 19.
2. Fereidouni Z, Dehghan Abnavi S, Ghanbari Z, Gashmard R, Zarepour F, Khalili Samani N et al. The impact of cancer on mental health and the importance of supportive services. Galen Med J. 2024;13:e3327.
3. Hutten RJ, Weil CR, King AJ, Barney B, Bylund CL, Fagerlin A, et al. Multi-institutional analysis of cancer patient exposure, perceptions, and trust in information sources regarding complementary and alternative medicine. JCO Oncol Pract. 2023;19(11):1000-1008.
4. Yun H, Sun L, Mao JJ. Growth of integrative medicine at leading cancer centers between 2009 and 2016: a systematic analysis of NCI-designated comprehensive cancer center websites. J Natl Cancer Inst Monogr. 2017;(52):lgx004.
5. Witt CM, Balneaves LG, Cardoso MJ, Cohen L, Greenlee H, Johnstone P, et al. A comprehensive definition for integrative oncology. J Natl Cancer Inst Monogr. 2017:3-8.
6. Bower JE, Lacchetti C, Alici Y, Barton DL, Bruner D, Canin BE, et al. Management of fatigue in adult survivors of cancer: ASCO-Society for Integrative Oncology guideline update. J Clin Oncol. 2024;42(20):2456-2487.
7. Braun IM, Bohlke K, Abrams DI, Anderson H, Balneaves LG, Bar-Sela G, et al. Cannabis and cannabinoids in adults with cancer: ASCO guideline. J Clin Oncol. 2024;42(13):1575-1593.
8. Carlson LE, Ismaila N, Addington EL, Asher GN, Atreya C, Balneaves LG, et al. Integrative oncology care of symptoms of anxiety and depression in adults with cancer: Society for Integrative Oncology-ASCO guideline. J Clin Oncol. 2023;41(28):4562-4591.
9. Mao JJ, Ismaila N, Bao T, Barton D, Ben-Arye E, Garland EL, et al. Integrative medicine for pain management in oncology: Society for Integrative Oncology-ASCO guideline. J Clin Oncol. 2022;40(34):3998-4024.
10. Society for Integrative Oncology. Training modules [Internet]. Available from: https://integrativeonc.org/training-modules/. Accessed 2026 Feb 24.
11. Hershman DL, Unger JM, Greenlee H, Capodice JL, Lew DL, Darke AK, et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial. JAMA. 2018;320:167-176.
12. Al Maqbali M, Al Sinani M, Al Naamani Z, Al Badi K, Tanash MI. Prevalence of fatigue in patients with cancer: a systematic review and meta-analysis. J Pain Symptom Manage. 2021;61:167-189.e14.
13. Stefanopoulou E, Grunfeld EA. Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors: a systematic review. J Psychosom Obstet Gynaecol. 2017;38(3):210-225.

14. Han J, Shi M, Bi LN, Wang LL, Cai YX. Efficacy of mind-body therapies for sleep disturbance in patients with early-stage cancer: a systematic review and network meta-analysis. Psychooncology. 2023;32(9):1315-1338.
15. Li K, Cai Y, Xie S, Zhou Y, Dong J, Zhu Q, et al. Evidence summary for nonpharmacological management of chemotherapy-induced nausea and vomiting. Biomed Res Int. 2022:4741193.
16. Lyman GH, Greenlee H, Bohlke K, Bao T, DeMichele AM, Deng GE, et al. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. J Clin Oncol. 2018;36:2647-2655.
17. Khamdi S, Matangkasombut O, Lam-Ubol A. Non-pharmacologic interventions for management of radiation-induced dry mouth: a systematic review. Oral Dis. 2024;30(5):2876-2893.
18. Misiąg W, Piszczyk A, Szymańska-Chabowska A, Chabowski M. Physical activity and cancer care—a review. Cancers (Basel). 2022;14(17):4154.
19. Courneya KS, Vardy JL, O'Callaghan CJ, Gill S, Friedenreich CM, Wong RKS, et al. Structured exercise after adjuvant chemotherapy for colon cancer. N Engl J Med. 2025;393(1):13-25.
20. Denlinger CS, Sanft T, Baker KS, Broderick G, Demark-Wahnefried W, Friedman DL, et al. Survivorship, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16:1216-1247.
21. Lee E, Kady V, Han E, Montan K, Normuminova M, Rovito MJ. Healthy eating and mortality among breast cancer survivors: a systematic review and meta-analysis of cohort studies. Int J Environ Res Public Health. 2022;19(13):7579.
22. Chen G, Leary S, Niu J, Perry R, Papadaki A. The role of the Mediterranean diet in breast cancer survivorship: a systematic review and meta-analysis of observational studies and randomised controlled trials. Nutrients. 2023;15(9):2099.
23. George SM, Alfano CM, Neuhouser ML, Smith AW, Baumgartner RN, Baumgartner KB, et al. Better postdiagnosis diet quality is associated with less cancer-related fatigue in breast cancer survivors. J Cancer Surviv. 2014;8(4):680-687.
24. Stobäus N, Müller MJ, Küpferling S, Schulzke JD, Norman K. Low recent protein intake predicts cancer-related fatigue and increased mortality in patients with advanced tumor disease undergoing chemotherapy. Nutr Cancer. 2015;67(5):818-824.
25. Zick SM, Colacino J, Cornellier M, Khabir T, Surnow K, Djuric Z. Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial. Breast Cancer Res Treat. 2017;161(2):299-310.
26. Sathiaraj E, Afshan K, Sruthi R, Jadoni A, Murugan K, Patil S, et al. Effects of a plant-based high-protein diet on fatigue in breast cancer patients undergoing adjuvant chemotherapy—a randomized controlled trial. Nutr Cancer. 2023;75(3):846-856.
27. American Institute for Cancer Research. Healthy eating [Internet]. Available from: https://www.aicr.org/cancer-prevention/healthy-eating/. Accessed 2026 Feb 9.
28. Oh B, Butow P, Mullan B, Clarke S, Tattersall M, Boyer M, et al. Patient-doctor communication: use of complementary and alternative medicine by adult patients with cancer. J Soc Integr Oncol. 2010;8(2):56-64.
29. Akeeb AA, King SM, Olaku O, White JD. Communication between cancer patients and physicians about complementary and alternative medicine: a systematic review. J Integr Complement Med. 2023;29(2):80-98.
30. Pouchieu C, Fassier P, Druesne-Pecollo N, Zelek L, Bachmann P, Touillaud M, et al. Dietary supplement use among cancer survivors of the NutriNet-Santé cohort study. Br J Nutr. 2015;113(8):1319-1329.
31. D'Andre SD, Bauer BA, Hofmann MB, Burckhard JL, Montane HN, Loprinzi CL. Dietary supplement use and recommendations for discontinuation in an integrative oncology clinic. Support Care Cancer. 2022;31(1):40.
32. EfficaSafe website [Internet]. Available from: https://www.efficasafe.com/. Accessed 2026 Feb 19.
33. About Herbs website [Internet]. Available from: https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs. Accessed 2026 Feb 19.
34. NatMed database [Internet]. Available from: https://naturalmedicines.therapeuticresearch.com/Home/ND. Accessed 2026 Feb 19.
35. Hou YN, Chimonas S, Gubili J, Deng G, Mao JJ. Integrating herbal medicine into oncology care delivery: development, implementation, and evaluation of a novel program. Support Care Cancer. 2023;31(2):128.

doi.org/10.58931/cot.2026.3148

About the Authors

Bharath Gangadharaiah, MD

Dr. Bharath Gangadharaiah is a Medical Oncologist with a strong academic and research background in solid tumors, particularly breast and genitourinary cancers. Trained at AIIMS, New Delhi, he has contributed to multiple peer-reviewed publications and international collaborations. His research interests include real-world outcomes, clinical trials, and innovative systemic therapies.

Affiliations: CancerCare Manitoba, University of Manitoba, Winnipeg, MB, Canada

Jeffrey Graham, MD, MPH

Dr. Jeffrey Graham is a staff medical oncologist at CancerCare Manitoba, assistant professor in the department of internal medicine at the University of Manitoba, chair of the provincial genitourinary disease site group, and affiliate scientist at the CancerCare Manitoba Research Institute.

Affiliations: CancerCare Manitoba, University of Manitoba, Winnipeg, MB, Canada

HIF Inhibition and Emerging Therapeutic Targets in Clear Cell Renal Cell Carcinoma

Bharath Gangadharaiah, MD
Jeffrey Graham, MD, MPH

Abstract

Clear cell renal cell carcinoma (ccRCC) is characterized by inactivation of the von Hippel-Lindau (VHL) pathway, resulting in stabilization of hypoxia-inducible factors (HIFs) and activation of transcriptional programs involved in angiogenesis, metabolism, and tumour survival. This biology established HIF-2α as a rational therapeutic target and led to the development of belzutifan, the first HIF-2 inhibitor to demonstrate randomized clinical benefit in ccRCC. In this review, we summarize the biologic rationale for HIF inhibition in ccRCC, review the key data supporting belzutifan with a focus on the LITESPARK-005, LITESPARK-011, and LITESPARK-022 studies, discuss next-generation HIF-2 inhibitors, including casdatifan, and briefly highlight other emerging therapeutic targets in ccRCC.

Introduction

Clear cell renal cell carcinoma (ccRCC) is characterized by dysregulation of the von Hippel-Lindau (VHL)/hypoxia-inducible factor (HIF) axis, resulting in stabilization of HIF-α subunits and activation of transcriptional programs involved in angiogenesis, proliferation, erythropoiesis, and metabolic adaptation.[1,2] This biology provided the foundation for vascular endothelial growth factor (VEGF)-directed therapy, but also identified HIF-2α as a more proximal and disease-specific

therapeutic target. Belzutifan, the first HIF-2 inhibitor to demonstrate clinical benefit in ccRCC, has expanded the treatment landscape beyond VEGF receptor tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICI).[3]

This review summarizes the biological rationale for HIF-2 inhibition in ccRCC and reviews the key clinical data supporting belzutifan, with emphasis on the LITESPARK-005, LITESPARK-011, and LITESPARK-022 clinical trials. It also briefly discusses next-generation HIF-2 inhibitors, particularly casdatifan, and outlines other emerging non-HIF therapeutic targets under investigation in ccRCC.

Biologic Rationale for HIF-2 Inhibition

Loss of VHL function is a defining molecular event in most ccRCCs. Under normal oxygen conditions, VHL targets HIF-α subunits for ubiquitin-mediated degradation. When VHL is inactivated, HIF accumulates and drives expression of genes involved in tumour growth and survival, including *VEGF*, *GLUT1*, *CXCR4*, and cyclin D1 (*CCND1*).[1] Although both HIF-1α and HIF-2α contribute to hypoxia signalling, preclinical and translational data support HIF-2α as the more relevant therapeutic target in many ccRCC tumours.[2] HIF-2 inhibition is therefore distinct from conventional antiangiogenic therapy, as it targets a proximal transcriptional driver upstream of multiple downstream programs.

This biology also provides a rationale for combination strategies and for evaluation in earlier disease settings. Combining HIF-2 inhibition with VEGF-directed therapy may enhance pathway suppression by targeting both the upstream driver and downstream angiogenic signalling. There is also interest in moving HIF-2 inhibition to earlier lines of treatment, when tumours may remain more dependent on VHL/HIF biology and before the emergence of resistance mechanisms associated with prior systemic therapy.

Belzutifan: A First-in-class HIF Inhibitor

Early proof-of-concept for belzutifan came from germline/VHL disease-associated ccRCC, in which it showed durable activity and manageable toxicity, demonstrating that HIF-2 could be safely inhibited.[2] The key question, however, was whether this biology would translate to sporadic ccRCC.

In the LITESPARK-005 phase III trial, 746 patients with sporadic mRCC who had previously received both ICI and antiangiogenic therapy were randomized to belzutifan or everolimus.[3] Median progression-free survival (PFS) was 5.6 months in both arms, but the curves separated over time, with a 24-month PFS of 17.5% for the belzutifan arm versus 4.1% for the everolimus arm. The objective response rate was 21.9% versus 3.5%, and median overall survival (OS) was 21.4 versus 18.1 months, respectively; the difference in OS was not statistically significant.[3] The improved landmark PFS suggests that there is a subset of tumours that remain dependent on HIF activity and may experience durable disease control. These data established belzutifan as a clinically relevant option in patients with ICI/anti-VEGF-refractory sporadic metastatic RCC (mRCC). Importantly, patient-reported outcomes from the LITESPARK-005 trial also favoured belzutifan, with better disease-related symptom control and global quality of life relative to everolimus.[4]

The characteristic toxicities of belzutifan largely reflect on-target biology. Anemia is a

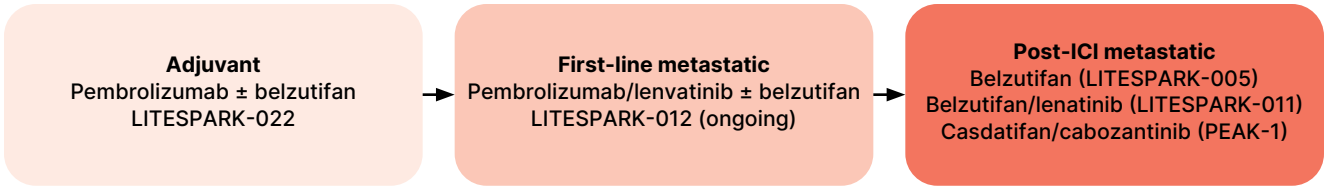

Figure 1. Positioning HIF-2 inhibition across the ccRCC disease continuum, including belzutifan in first-line development (LITESPARK-012), post-PD-(L)1 therapy (LITESPARK-005 and -011), and the adjuvant setting (LITESPARK-022); *courtesy of Bharath Gangadharaiah, MD, and Jeffrey Graham, MD, MPH.*

Abbreviations: ccRCC: clear cell renal cell carcinoma; **HIF-2:** hypoxia-inducible factor 2; **ICI:** immune checkpoint inhibitors; **PD-1:** programmed cell death protein 1; **PD-L1:** programmed cell death ligand 1

common adverse event (AE), as HIF signalling regulates erythropoietin homeostasis. Hypoxia is another common AE and is thought to reflect the drug's impact on oxygen sensing and ventilatory adaptation. In the LITESPARK-005 study, grade ≥3 AEs occurred at similar rates in both arms, but discontinuation due to AEs was lower with belzutifan (5.9%) than with everolimus (14.7%).[3] In practice, anemia and hypoxia require close monitoring, but the safety profile is generally manageable with drug holds and dose reductions. Notably, anemia in the belzutifan arm was managed with an erythropoiesis-stimulating agent alone in 16.7% of participants, blood transfusion alone in 18.5%, and both in 11.3%, supporting the feasibility of continued treatment with appropriate supportive care. Hypoxia occurred in 14.5% of participants receiving belzutifan, with grade ≥3 events in 10.5%, and oxygen therapy was required in 14.5% of participants receiving belzutifan, with grade ≥3 in 5%, and oxygen therapy was required in 10.2%, underscoring the need for vigilance while confirming that these toxicities are usually managed with appropriate intervention.

Belzutifan Combinations and Earlier-line Development: The LITESPARK-011, LITESPARK-022, and LITESPARK-012 Trials

Two phase III trials have reported efficacy data for belzutifan-based combinations in ccRCC: the LITESPARK-011 trial provided evidence for use in previously treated advanced disease, while the LITESPARK-022 study assessed use in the adjuvant setting.

In LITESPARK-011, patients with advanced RCC progressing after anti-PD-(L)1 therapy were randomized to belzutifan plus lenvatinib or cabozantinib.[5] At a median follow-up of 29.0 months, belzutifan plus lenvatinib improved PFS compared with cabozantinib (hazard ratio [HR]: 0.70), with median PFS of 14.8 versus 10.7 months. The objective response rate was also higher with the combination (52.6% vs. 40.2%), as was the duration of response (23 months vs. 12.3 months). Interim OS analysis numerically favoured belzutifan plus lenvatinib (HR: 0.85), but

Trial	Setting	Intervention / comparator	Key efficacy signal	Development status
LITESPARK-005	Post-ICI and antiangiogenic therapy	Belzutifan vs. everolimus	18-mo PFS: 24.0% vs. 8.3%; ORR: 21.9% vs. 3.5%; median OS: 21.4 vs. 18.1 mo	Phase III positive for PFS
LITESPARK-011	After anti-PD-(L)1 therapy	Belzutifan + lenvatinib vs. cabozantinib	Median PFS: 14.8 vs. 10.7 mo; HR: 0.70; ORR: 52.6% vs. 40.2%	Phase III positive; OS immature
LITESPARK-022	Adjuvant intermediate-high risk / high risk / M1 NED	Pembrolizumab + belzutifan vs. pembrolizumab + placebo	24-mo DFS: 80.7% vs. 73.7%; HR: 0.72	Phase III positive; OS immature
LITESPARK-012	First-line metastatic	Pembrolizumab + lenvatinib vs. pembrolizumab + lenvatinib + belzutifan vs. pembrolizumab + quavonlimab + lenvatinib	Primary endpoints: PFS and OS	Ongoing phase III
PEAK-1	After prior PD-(L)1 therapy	Casdatifan + cabozantinib vs. placebo + cabozantinib	Registrational study of next-generation HIF-2 inhibitor	Ongoing phase III

Table 1. Key HIF-2–directed trials in ccRCC; *courtesy of Bharath Gangadharaiah, MD, and Jeffrey Graham, MD, MPH.*

Abbreviations: ccRCC: clear cell renal cell carcinoma; **DFS:** disease-free survival; **HIF-2:** hypoxia-inducible factor 2; **HR:** hazard ratio; **ICI:** immune checkpoint inhibitors; **M1 NED:** metastatic with no evidence of disease; **mo:** months; **ORR:** objective response rate; **OS:** overall survival; **PD-1:** programmed cell death protein 1; **PD-L1:** programmed cell death ligand 1; **PFS:** progression-free survival.

these data remain immature.[5] Grade ≥3 treatment-related AEs occurred in 71.6% of patients receiving belzutifan plus lenvatinib and were comparable to those associated with cabozantinib (65.8%).[5] These findings support further development of belzutifan-based combinations in previously treated ccRCC, although longer follow-up, particularly for OS, will be important. The higher ORR and longer duration of response suggest a subgroup of patients can achieve prolonged disease control, making this combination an attractive option post-ICI, pending regulatory approval.

LITESPARK-022 was a randomized phase III trial in patients with resected intermediate-high-risk, high-risk, or stage M1 with no evidence of disease (NED; defined as metachronous solitary metastasis completely resected within 2 years of primary nephrectomy) ccRCC, comparing adjuvant pembrolizumab plus belzutifan with pembrolizumab plus placebo.[6] This study builds on KEYNOTE-564, which established pembrolizumab as the current standard of treatment in the adjuvant setting. At a median follow-up of 28.4 months, disease-free survival favoured the belzutifan arm (HR: 0.72), and 24-month disease-free survival was 80.7% in the belzutifan arm versus 73.7% for the placebo arm. Median disease-free survival was not reached in either arm, and OS data remain immature.[6] Grade ≥3 treatment-related AEs were more frequent with pembrolizumab plus belzutifan than with pembrolizumab alone (52.1% vs. 30.2%), with anemia and hypoxia contributing to this difference.[6] These results are encouraging, but longer follow-up will be needed to determine whether the disease-free survival benefit is maintained and if this translates into improved OS. Given the added toxicity and potential for overtreatment in the adjuvant setting, demonstrating an OS benefit will be important for defining the risk-benefit profile of this combination.

LITESPARK-012 is an ongoing phase III first-line study evaluating pembrolizumab plus lenvatinib with the addition of belzutifan or quavonlimab in treatment-naïve mRCC.[7] Although efficacy data are not yet available, the first-line setting is an important space to test belzutifan. Tumours may be more dependent on VHL/HIF-driven biology before exposure to prior systemic therapy and the emergence of treatment-related resistance. In addition, incorporating belzutifan into a pembrolizumab/lenvatinib backbone may provide a mechanistically distinct strategy to improve depth and durability of response.[7]

Platform / target	Example	Stage	Current role in ccRCC
PD-1/VEGF bispecific	Ivonescimab (IVORY)	Phase II	Conceptually attractive; RCC efficacy not yet established
ENPP3 × CD3 bispecific	XmAb819	Phase I	Early dose-escalation/expansion in relapsed or refractory ccRCC
CD70-directed cellular therapy	CTX130	Phase I	Proof of concept shown; durability and scalability remain open questions
Individualized neoantigen vaccine	V940 + pembrolizumab (INTerpath-004)	Phase II	Adjuvant strategy under active evaluation
Other oral immune modulators	HPK1 / PTPN2 programs	Early phase	Interesting biology but no definitive RCC efficacy signal yet

Table 2. Selected emerging non-HIF targets in ccRCC; *courtesy of Bharath Gangadharaiah, MD, and Jeffrey Graham, MD, MPH.*

Abbreviations: ccRCC: clear cell renal cell carcinoma; **ENPP3:** Ectonucleotide pyrophosphatase / phosphodiesterase 3; **HIF:** hypoxia-inducible factor; **VEGF:** vascular endothelial growth factor.

Other HIF-2 Inhibitors: How Does Casdatifan Compare?

Belzutifan remains the only approved HIF-2 inhibitor in ccRCC and is supported by randomized phase III studies. Casdatifan is the leading next-generation HIF-2 inhibitor in development. Early studies suggest that casdatifan has clinical activity in previously treated ccRCC and may offer flexibility for combination development, but there are currently no direct comparative data with belzutifan.[8-11] At present, belzutifan remains the only HIF-2 inhibitor with mature phase III efficacy data in ccRCC.

In the phase I ARC-20 study, casdatifan monotherapy showed encouraging activity in previously treated ccRCC, and updated analyses supported 100 mg once daily as the preferred development dose.[8,9] Casdatifan plus cabozantinib has also shown promising early activity, leading to the ongoing phase III PEAK-1 trial.[12] PEAK-1 is evaluating casdatifan plus cabozantinib versus placebo plus cabozantinib in patients with advanced or metastatic ccRCC that has progressed on or after prior anti-PD-1/PD-L1 therapy, with PFS as the primary endpoint. The study design is similar to that of the LITESPARK-011 trial and may provide data for a second HIF-based combination strategy in refractory mRCC.

Data on other HIF-targeting agents remain limited. DFF332 showed modest phase I activity, and its future development in ccRCC remains uncertain.[1] NKT2152 is still in early-phase development, and currently available clinical data are too limited to place it alongside belzutifan or casdatifan.[13]

An important limitation across HIF-2 drug development is the lack of validated predictive biomarkers. At present, there are no established molecular or clinical markers that reliably identify which patients are most likely to derive durable benefit from belzutifan or other HIF-2 inhibitors.[3,9] Although translational analyses are ongoing, treatment selection remains empirical, and biomarker development should remain an important priority for future trials.

Other Emerging Non-HIF Targets in ccRCC

Although HIF-2 inhibition is the most clinically relevant novel target in ccRCC, the broader pipeline continues to expand. One example is anti-PD-1/VEGF bispecific therapy. The phase II IVORY trial is evaluating ivonescimab in patients with previously treated advanced or metastatic ccRCC who received prior ICI treatment.[14] This approach is of interest because it combines both PD-1 and VEGF pathway inhibition within a single molecule, although clinical data in RCC remain limited.

Additional immunotherapy-based strategies are also under investigation. XmAb819, an ENPP3 × CD3 bispecific antibody, is being evaluated in a phase I study in relapsed or refractory ccRCC and is supported by the relatively high ENPP3 antigen expression in this disease.[15,16] Early clinical experience remains preliminary.

CD70-directed cellular therapy is further along in development. In a phase I study, the allogeneic chimeric antigen receptor (CAR)-T cell product CTX130 demonstrated disease control in a substantial proportion of treated patients with advanced ccRCC, including a durable complete response in one patient.[17] Finally, individualized neoantigen vaccination is being studied in the adjuvant setting. INTerpath-004 is evaluating the ICI pembrolizumab with or without the mRNA-based vaccine V940 in patients with RCC at increased risk of recurrence after nephrectomy.[16] Overall, these approaches remain investigational and should be considered only in the context of clinical trials.

Conclusions

HIF-2 inhibition has evolved from a biological concept in ccRCC to a clinically relevant therapeutic strategy. Belzutifan is now supported by randomized data in advanced and adjuvant ccRCC.[3,4] Results from the LITESPARK-011 and LITESPARK-022 studies suggest that further development of HIF-2 inhibition will likely focus on combination approaches and use in earlier disease settings, although OS and longer-term outcome data remain immature.[5,6] LITESPARK-012 will be an important study in defining whether belzutifan has a role in the first-line setting.[7] Casdatifan is the leading next-generation HIF-2 inhibitor in development and is currently being evaluated in the ongoing phase III PEAK-1 trial.[8-10] At present, HIF-2 inhibition has become an important component of the therapeutic landscape in ccRCC, whereas bispecific antibodies, cellular therapies, and individualized vaccines remain in earlier stages of clinical development.

Correspondence

Jeffrey Graham, MD, MPH
Email: jgraham9@cancercare.mb.ca

Financial Disclosures

B.G.: None declared.
J.G.: Advisory board/consultancy: Ipsen, Pfizer, Merck, BMS, Janssen, Bayer, Emd Serono.

References

1. Kaelin WG Jr. The von Hippel-Lindau tumor suppressor protein and clear cell renal carcinoma. Clin Cancer Res. 2007;13(2 Pt 2):680s-684s.
2. Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. N Engl J Med. 2021;385(22):2036-46.
3. Choueiri TK, Albiges L, Burotto M, McDermott DF, Motzer RJ, Powles T, et al. Belzutifan versus everolimus for advanced renal-cell carcinoma. N Engl J Med. 2024;391(10):883-95.
4. Powles T, Albiges L, Burotto M, McDermott DF, Motzer RJ, Choueiri TK, et al. Health-related quality of life with belzutifan versus everolimus for advanced renal cell carcinoma (LITESPARK-005): patient-reported outcomes from a randomised, open-label, phase 3 trial. Lancet Oncol. 2025;26(4):491-502.
5. Motzer RJ, Bilen MA, McGregor BA, Escudier B, Ravaud A, Bedke J, et al. Belzutifan plus lenvatinib versus cabozantinib for advanced renal cell carcinoma after anti-PD-(L)1 therapy: open-label phase 3 LITESPARK-011 study. J Clin Oncol. 2026;44(7_suppl):LBA417.
6. Choueiri TK, Motzer RJ, Powles T, Burotto M, Bedke J, Lee CH, et al. Adjuvant pembrolizumab plus belzutifan versus pembrolizumab for clear cell renal cell carcinoma: randomized phase 3 LITESPARK-022 study. J Clin Oncol. 2026;44(7_suppl):LBA418.
7. Choueiri TK, Powles T, Voss MH, Plimack ER, Gurney H, Song Y, et al. LITESPARK-012: pembrolizumab plus lenvatinib with or without belzutifan or quavonlimab for advanced renal cell carcinoma. Future Oncol. 2023;19(40):2631-40.
8. Lee JL, Ornstein MC, McGregor BA, Barata PC, Voss MH, Ravaud A, et al. Casdatifan monotherapy in patients with previously treated clear cell renal cell carcinoma: safety, efficacy and subgroup analysis across multiple doses from ARC-20, a phase 1 open-label study. J Clin Oncol. 2025;43(5_suppl):441.
9. Choueiri TK, Ornstein MC, Barata PC, Kumar R, Lee J, McGregor BA, et al. Activity and biomarker analyses with casdatifan, a next-generation HIF-2α inhibitor, in refractory clear cell renal cell carcinoma: results from ARC-20. J Clin Oncol. 2026;44(7_suppl):493.
10. Schweickert PG, Ahmadi L, Junu C, Chhabra S, Sykes D, Vu C, et al. Casdatifan (AB521) is a novel and potent allosteric small molecule inhibitor of protumourigenic HIF-2α dependent transcription. Br J Pharmacol. 2025;182(17):4147-67.
11. Ghasemi M, Khosravan R, Agoram B, Kim JY, Kumar R, Higa GM, et al. Pharmacokinetics, pharmacodynamics and safety of casdatifan, a novel hypoxia-inducible factor-2α inhibitor, in healthy participants. Br J Clin Pharmacol. 2025;91(2):1000-13.
12. Choueiri TK, Ornstein MC, Barata PC, Matrana MR, Merchan JR, Gedye C, et al. Combination casdatifan plus cabozantinib expansion cohort of phase 1 ARC-20 study in previously treated patients with clear cell renal cell carcinoma. J Clin Oncol. 2025;43(16_suppl):4506.
13. Jonasch E, Hauke R, Falchook G, Logan T, Gordon M, Hall E, et al. A phase 1/2, open label dose-escalation and expansion trial of NKT2152 in adults with advanced clear cell renal cell carcinoma. J Clin Oncol. 2023;41(16_suppl):TPS4607.
14. Dizman N, Slack-Tidwell RS, Sheth RA, Alhalabi O, Campbell MT, Corn PG, et al. Phase II trial of ivonescimab in patients with advanced clear cell renal cell carcinoma previously treated with immune checkpoint blockade: IVORY trial (NCT06940518). Oncologist. 2025;30(Suppl 2):oyaf276.021.
15. Bohac C, Pal S, Sweis R, Kotecha R, Runcie K, Bilen M, et al. A phase 1, multiple-dose study to evaluate the safety and tolerability of first-in-class XmAb819 (ENPP3 × CD3) in subjects with relapsed or refractory clear cell renal cell carcinoma. Oncologist. 2025;30(Suppl 2):oyaf276.018.
16. Doñate F, Raitano A, Morrison K, An Z, Capo L, Avina H, et al. AGS16F is a novel antibody-drug conjugate directed against ENPP3 for the treatment of renal cell carcinoma. Clin Cancer Res. 2016;22(8):1989-99.
17. Pal SK, Becerra CR, Tykodi SS, Costello JC, Lee CH, Lee S, et al. CD70-targeted allogeneic CAR T-cell therapy for advanced clear cell renal cell carcinoma. Cancer Discov. 2024;14(7):1176-89.


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