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The Management of Advanced Anal Squamous Cell Carcinoma

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The Management of Advanced Anal Squamous Cell Carcinoma

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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)- γ 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	$\geq 2L$	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	$\geq 2L$	112	Pembrolizumab (single-arm trial)	11% (6-18)	2.0	12.0
NCI9673 – Part B ²³	Refractory metastatic ASCC	$\geq 2L$	37	Nivolumab $\pm$ 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/m² 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/m² 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 progressed 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.

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Metastatic CRPC: Contemporary Therapeutic Options and Optimal Sequencing

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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 $\geq 50\%$ 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 *BRCA1/2*) 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

lasting 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 (²²³Ra) demonstrated improved OS and delayed skeletal-related events in the ALSYMPCA trial for patients with symptomatic bone-only mCRPC.⁴¹ ²²³Ra 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 ²²³Ra 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.

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Second-line Treatment Strategies in Biliary Tract Cancers

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Introduction

Biliary tract cancers (BTCs) are a highly heterogeneous 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:

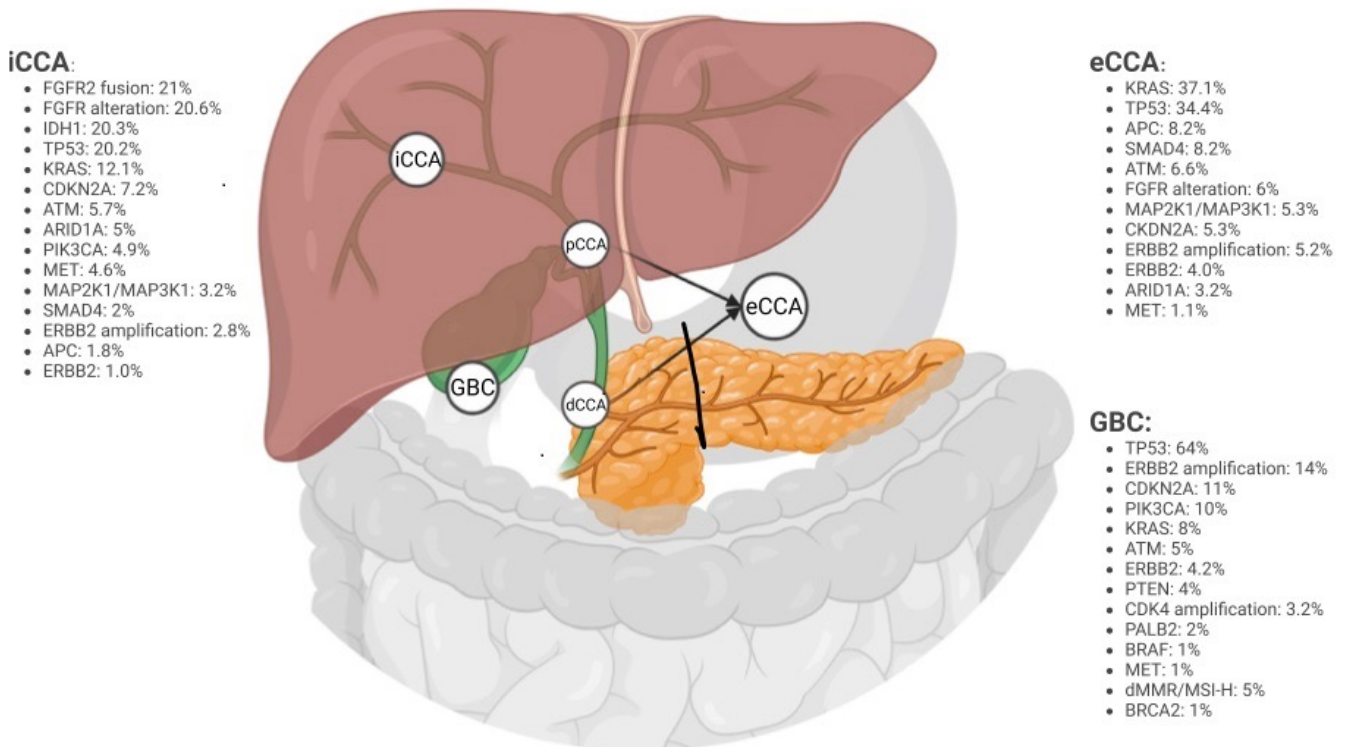


Figure 1. Biliary tract cancer molecular alteration prevalence by subtype¹⁵; courtesy of Giulia Pool, MD, and Janine M. Davies, MD, BN, MSc, FRCPC.

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	Larotrectinib 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 responses²⁰, 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%

Phase II studies in metastatic gastric cancer							
Drug	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 *ERBB2* 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 $\geq 50\%$ 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 inpatient 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.

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

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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.
- Practitioners 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, acupuncture, 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 After Treatment

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 EfficSafe,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.

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

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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-2 α 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-2 α 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-1 α and HIF-2 α contribute to hypoxia signalling, preclinical and translational data support HIF-2 α 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

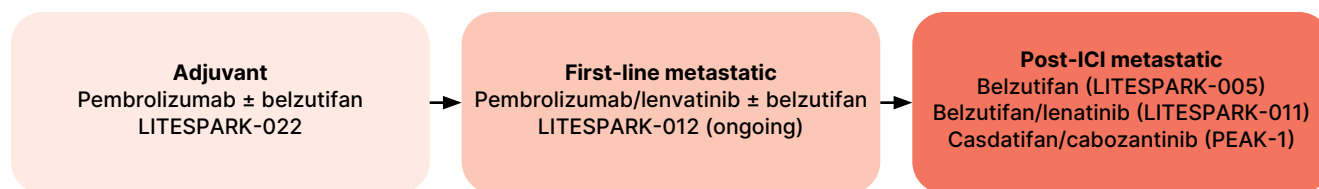


Figure 1. Positioning HIF-2 inhibition across the ccRCC disease continuum, including belzutifan in first-line development (LITESPARK-012), post-PD-(L)1 therapy (LITESPARK-005 and -011), and the adjuvant setting (LITESPARK-022); courtesy of Bharath Gangadharaiya, MD, and Jeffrey Graham, MD, MPH.

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 + 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 $\times$ 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.

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