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First-line Treatment Selection for Advanced Hepatocellular Carcinoma

Zainab Al Maqrashi, MD, MSc
Brandon M. Meyers, MD, MSc, FRCPC

Introduction

The treatment landscape of advanced/unresectable hepatocellular carcinoma (uHCC) has rapidly evolved since 2018. Over recent years, various systemic therapies and treatment approaches have been explored. Systemic therapy has primarily relied on tyrosine kinase inhibitors (TKIs); however, immune checkpoint inhibitors (ICIs) have more recently entered the realm of the treatment armamentarium.

Overview

First-line Treatment

TKI Monotherapy

The first therapeutic intervention that demonstrated improved survival rates in uHCC was sorafenib. The SHARP trial demonstrated overall survival (OS) improvements for sorafenib as compared to placebo (10.7 vs. 7.9 months) (hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.55-0.87; p<0.001).[1] In the decade following sorafenib's approval, numerous trials assessing systemic treatments for uHCC failed. In 2018, lenvatinib, another TKI, exhibited comparable OS to sorafenib in the non-inferiority REFLECT study (13.6 vs. 12.3 months), leading to lenvatinib's approval as an alternative option to sorafenib in the first-line setting. Interestingly, all other endpoints, including progression-free survival (PFS) (HR: 0.66; 95% CI: 0.57-0.77) and objective response rate (ORR) (OR 3.34; 95% CI: 2.17–5.14), and the adverse event profile, favoured lenvatinib.[2]

ICI-based combination therapy

The Phase III IMbrave150 trial compared atezolizumab plus bevacizumab with sorafenib, enrolling 501 previously untreated patients with advanced uHCC and well-compensated cirrhosis (Child-Pugh class A). Patients had to have baseline esophagogastroduodenoscopy (EGD) within six months before inclusion, with appropriate variceal disease management.[3] In their most recent analysis[4], combination therapy showed significantly improved median OS (19.2 vs. 13.4 months, HR: 0.66; 95% CI: 0.52-0.85). The ORR was three times higher for the combination therapy than sorafenib (30% vs. 11%). At 18 months, 51% of patients with uHCC receiving combination therapy continued to have a response, whereas the rate for sorafenib was 22%. Both groups experienced similar rates of treatment-related grade 3 or 4 adverse events (43% vs. 46%).

The HIMALAYA trial enrolled patients with uHCC and randomized them to receive either a single dose of the anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody tremelimumab alongside regular doses of the anti-programmed cell death ligand 1 (PD-L1) monoclonal antibody durvalumab, durvalumab monotherapy, or sorafenib. Durvalumab monotherapy was found to be non-inferior to sorafenib. Moreover, the primary analysis revealed a significant improvement in OS with tremelimumab plus durvalumab compared to sorafenib (16.4 vs. 13.8 months, HR: 0.78; 96% CI 0.65–0.93). From the perspective of ORR, the dual immunotherapy arm was superior to sorafenib (20.1% vs. 5.1%). At 4 years of follow-up, the incidence of serious treatment-related adverse events was 17.5% and 9.6% for patients in the combination immunotherapy and sorafenib groups, respectively.[5,6]

First-line treatment options continue to broaden. The Phase III CheckMate-9DW trial, assessing nivolumab plus ipilimumab for first-line therapy in uHCC carcinoma without prior systemic therapy, has successfully met its primary endpoint by demonstrating an OS advantage compared to the investigator's TKI choice (sorafenib or lenvatinib). Recently presented results have reflected improvement in ORR and median duration

of response as well.[7] Rate of treatment-related toxicity was consistent with previously reported data in combination ICI therapy.

Treatment selection

First-line Treatment

Immunotherapy-based combination therapy has shifted the landscape of uHCC management in the last decade. However, the approach

Agent(s)	Schedule	OS	PFS	Toxicity profile	Special considerations
Sorafenib[1]	Oral, twice daily	10.7 vs. 7.9 months	5.5 vs. 2.8 months	• Diarrhea • Hand-foot syndrome • Hypertension	In our opinion can be used as a later line therapy
Lenvatinib[2]	Oral, daily	13.6 vs. 12.3 months	7.4 vs. 3.7 months	• Hypertension	
Atezolizumab plus bevacizumab[3,4]	Intravenous, 21-day cycle	19.2 vs. 13.4 months	6.9 vs. 4.3 months	• Grade 3/4 TRAEs 43% • Incidence of upper gastrointestinal bleeding 7%	• Patients with MVI were included • Highest ORR (30%) • Pre-treatment EGD recommended for all patients
Tremelimumab/ durvalumab[5,6]	• Intravenous, tremelimumab x1, • Durvalumab every 28 days	16.4 vs. 13.7 months	3.8 vs. 4.1 months	• Grade 3/4 immune-mediated TRAEs 12.6%	• Longest follow-up data (4 years) • DOR 22.3 months
Nivolumab plus ipilimumab[7]	Intravenous, combination every 21 days for 4 cycles then maintenance Nivolumab every 28 days for maximum of 2 years	23.7 vs. 20.6 months	NA	• Grade 3/4 immune-mediated TRAEs 41%	• Highest ORR (36%) • DOR 30.4 months

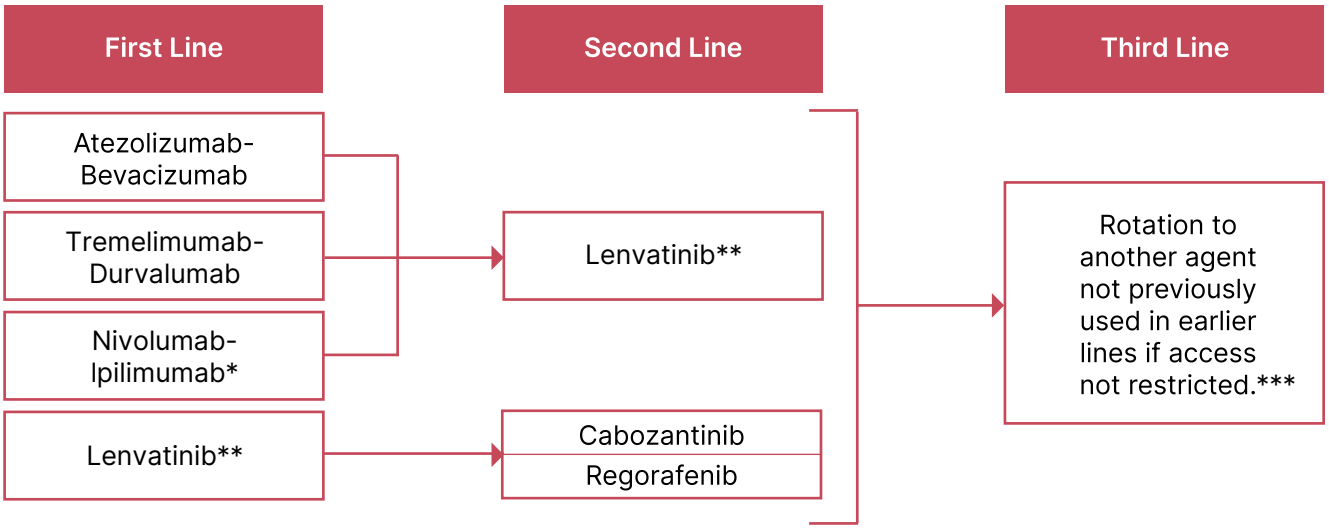
Table 1. Key factors in the treatment selection for patients with uHCC in the first-line setting; *courtesy of Zainab Al Maqrashi, MD, MSc and Brandon M. Meyers, MD, MSc, FRCPC*
Abbreviations: DOR: duration of response; **EGD:** esophagogastroduodenoscopy; **MVI:** microvascular invasion; **ORR:** objective response rate; **OS:** overall survival; **PFS:** progression-free survival; **TRAE:** treatment-related adverse events; **uHCC:** advanced/unresectable hepatocellular carcinoma.

to selecting first-line therapy is a complex, multifaced decision due to the lack of head-to-head comparison between different regimens and reliance on cross-trial comparisons **(Table 1)**.

First, factors related to accessibility, route of administration, and treatment convenience will prove valuable in therapy selection, especially from the patient's perspective. However, the data would indicate that patients suitable to receive ICI should receive one in the first-line setting due to the magnitude of benefit in OS, and in the Canadian landscape that ICI can only be given in the first-line setting.

Second, there are disease-related factors to be considered, including pre-existing unfavourable tumour biology, such as hepatic reserve, the burden of metastatic disease, and locoregional vascular invasion. In the IMbrave150 trial, 39.9% of the study population had microvascular invasion (MVI) prior to randomization.[3] A subsequent subgroup analysis revealed that the OS advantage was observed across all subgroups, irrespective of MVI status.[4] Post-hoc exploratory analyses on patients in the IMbrave150 trial with high-risk MVI (defined by the presence of a tumour thrombus in the main trunk and/or contralateral portal vein) was performed. Initial observations indicated that the advantages of combining atezolizumab plus bevacizumab for this subset of patients were comparable across various efficacy measures. Nevertheless, statistical significance was not attained, probably due to the limited number of subjects.[8] On the other hand, there are no data on patients with main portal invasion using other first-line therapies post the SHARP era, who are typically excluded from trials. However, other therapies are in use in high-risk MVI with appropriate screening EGD on the basis that the risk of bleeding is both therapy-dependent and related to disease characteristics (e.g. MVI, prior varices, or low platelets).[9]

Third, screening for contraindications for immunotherapy (e.g. active autoimmune conditions or liver transplantation) and anti-angiogenic therapy (e.g. recent thrombotic events, high bleeding risk, or uncontrolled hypertension) should be performed carefully and should include assessment for potential drug-drug interactions. An area of interest is the safety of atezolizumab plus bevacizumab in terms of bleeding risk. In line with the pivotal trial selection criteria, we recommend baseline EGD wherever feasible. Recognizing accessibility challenges in rural and community centres, a careful risk-benefit discussion should be carried out with the patient with the aim to complete the screening study within 1-2 cycles of therapy initiation and perhaps hold bevacizumab until screening is completed in high-risk patients.



* Pending Health Canada/CADTH approval; ** If intolerant, Sorafenib; *** In most jurisdictions in Canada, therapy beyond second line is not funded, however, these agents could be used if accessible or paid out of pocket; Sorafenib can be used if no other options available.

Figure 1. Current provisionally funded systemic therapies for advanced/unresectable hepatocellular carcinoma; *courtesy of Zainab Al Maqrashi, MD, MSc and Brandon M. Meyers, MD, MSc, FRCPC*

Fourth, the predictability of the toxicity profile, its patterns, and its possible impact on quality of life (QoL) should be prioritized in the shared decision-making with patients. In the REFLECT study, patients on lenvatinib had lower dermatological toxicity and alopecia rates than those on sorafenib. However, this was accompanied by higher rates of Grade 3 or 4 drug-induced hypertension[2]. We suggest hypertension is the more easily managed toxicity, with less impact on QoL. In an independent examination of patient-reported outcome measures derived from the IMbrave150 trial, individuals treated with atezolizumab plus bevacizumab exhibited notably extended intervals before experiencing a decline in median time to QoL deterioration, physical functioning, and role functioning. Furthermore, this treatment was associated with a diminished likelihood of deterioration in disease-related symptoms when contrasted with sorafenib monotherapy.[10] These findings underscore the importance of incorporating these parameters in care planning. In our opinion, lenvatinib is the TKI of choice in the first-line setting compared to sorafenib based on its efficacy and toxicity profile. Deciding between ICI combinations is more challenging and comes down to a physician-patient discussion regarding risks and benefits.

Later Lines of Treatment

Treatment choices after progression on initial therapy should be guided by prior systemic therapy, established clinically meaningful advantages, predicted tolerability based on potential treatment-related adverse events, hepatic reserve, and functional status. **Figure 1** shows the currently provisionally funded systemic therapies for uHCC.

TKI have been well-studied post-progression on sorafenib. The placebo-controlled RESORCE trial suggested a benefit for regorafenib in this clinical setting in terms of the median OS (10.6 vs. 7.8 months, HR: 0.63; 95% CI: 0.50-0.79) and ORR (11% vs. 4%),[11] and mandated that enrolled patients be sorafenib tolerant (≥400 mg daily for at least 21 of the 28 days before discontinuation). Cabozantinib, another TKI, was studied in the Phase III CELESTIAL trial after prior sorafenib therapy in first- or second-line treatment, and demonstrated superiority in OS and PFS over placebo.[12] Adverse events related to both drugs in their respective trials have been consistent with earlier TKI reports with no new safety signals. Selection between the two drugs should be based on matching the patient's profile with the potential toxicity.

Subsequent lines of treatment in the era of new combination therapies are less well-defined as there are currently no Phase III data to support second-line treatment after first-line ICI-based therapy. Practically speaking, TKIs are used post-progression on ICIs, as supported by the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN) guidelines with consideration for ICI monotherapy or combination treatment, depending on accessibility and the patient's profile.[13-15] Owing to the individual differences in the targeted cellular proteins and signaling pathways between different TKIs, in the event of tumour progression, rotation to another agent not previously trialed in the first or second line is recommended.[16]

Future Directions

With the rapid evolution in the management of uHCC after the introduction of ICIs, multiple areas for exploration remain. There is a paucity of prospective evidence looking at predictive biological markers of response, and whether the underlying disease etiology is a factor. Moreover, whether the observed therapeutic benefits can be extended in patients with an intermediate functional status (Eastern Cooperative Oncology Group [ECOG][2] and borderline hepatic reserve (Child-Pugh B) remains unclear.

In second-line therapy, the ideal regimen after immunotherapy remains undefined, and further guidance from randomized clinical trials is awaited.

Based on the current guidelines, ICIs are contraindicated in solid organ transplant recipients, which limits treatment options for patients with recurrent uHCC post-transplant. The circumstances might evolve in the future.

There is a growing interest in solidifying the role of combination ablative local interventions alongside standard-of-care systemic therapy for managing uHCC, pending further maturation of evidence to guide clinical decision-making. Radioembolization with Yttrium-90 (90Y), in addition to sorafenib, did not offer any OS advantage in uHCC.[17] In comparison, the recently published LAUNCH trial examining the role of transarterial chemoembolization (TACE) in addition to lenvatinib in previously untreated patients with uHCC showed improved PFS and

OS in the experimental arm, with an observed benefit across different high local disease risk groups, such as tumour multiplicity, existing portal vein tumour thrombus, and tumours ≥5 cm.[18] On the other hand, in an attempt to examine non-invasive interventions, the NRG/RTOG 1112 study evaluated stereotactic body radiation therapy (SBRT) followed by sorafenib versus sorafenib monotherapy in patients with uHCC, of whom 74% had MVI. Due to changes in the standard of care in HCC, the accrual was prematurely closed. Based on preliminary reports, the SBRT arm experienced improved OS and PFS, with improvements in the QoL at 6 months post-treatment initiation.[19] In the EMERALD-1 study, embolization candidates among patients with uHCC were randomized to TACE combined with durvalumab with or without bevacizumab. Early results have shown improved PFS alongside an ORR of 43.6% in the triple intervention arm compared to 29.6% in the TACE only arm. The OS data is not available yet.[20] This trial reflects an attempt at expanding the role of ICI-based systemic therapy in addition to locoregional management in intermediate-stage disease. Full publications from these trials and others in the pipeline are awaited.

Conclusion

The last decade has witnessed significant improvements in systemic therapy for uHCC in addition to the established option of sorafenib with the introduction of lenvatinib and ICI-based combination options, including atezolizumab plus bevacizumab and tremelimumab plus durvalumab. Locally approved second-line options encompass TKIs, such as regorafenib and cabozantinib. The selection of therapy depends on individualized treatment goals and the patient's profile.

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Prostate-specific Membrane Antigen (PSMA): A Diagnostic and Therapeutic Target in Advanced Prostate Cancer

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Introduction

Prostate cancer is among the most prevalent malignant conditions globally, and both incidence and mortality are expected to increase markedly over the next two decades.[1] Recently, the diagnostic and treatment landscape for managing this disease underwent remarkable advances that led to the incorporation of innovative approaches, such as prostate-specific membrane antigen (PSMA) theranostics.[2]

PSMA, which is also known as folate hydroxylase or glutamate carboxypeptidase, is a transmembrane protein 100- to 1000-fold overexpressed by prostate cancer cells compared to healthy cells found in the benign prostate gland, salivary glands, proximal renal tubules, small intestine mucosa, and hepatocytes, amongst others.[3]

Since its discovery over 30 years ago (see **Figure 1** for this and other milestones), PSMA has caught the attention of the scientific community as a potential therapeutic target, and for the past two decades many efforts have been undertaken to identify and develop PSMA ligands and antibodies that could be exploited as prostate cancer therapeutics.[4]

This review aims to provide an overview of available PSMA ligands, their mechanisms of action, diagnostic and therapeutic applications, and future perspectives of PSMA-targeted therapeutic approaches within the field of radioligand therapy (RLT).

Mechanism of Action and Biology of PSMA Ligands

Isolated in 1993, the PSMA molecule is a 100 kDa protein encoded by the *FOLH1* gene on chromosome 11p11-12.[5] PSMA demonstrates resemblance with the transferrin receptor. Several mechanisms regulating its expression have been described to date, including co-expression/upregulation with the androgen receptor (AR) and modulation via epigenetic mechanisms. A proximal promoter and an enhancer site in the third intron are two important gene regulatory elements that have been described. Moreover, several transcription factors other than the AR play an important role in regulating PSMA expression.[5-8] Of particular interest is the relationship between PSMA expression and AR blockade, which has produced conflicting data.[9]

Structurally, the PSMA protein consists of three parts. The 707 amino acid extracellular portion contains a catalytic binding site - the enzymatic activity of which is modulated by the glycosylation of extracellular domains and by the interaction with actin-binding anchor protein filament A. Although it is hypothesized that enzymatic substrates, such as polyglutamated folate, are internalized by PSMA, specific biological ligands for PSMA remain unknown to date.[10] The mechanisms of PSMA-mediated internalization and interaction with the endosomal compartment are relevant because they are an important aspect of how small molecules and peptides bound to PSMA can exert their anticancer properties.[10]

The exact biological functions of PSMA remain to be elucidated. Besides being a tumour marker and an imaging target, the metabolites generated by its glutamate carboxypeptidase and N-acetylated a-linked acidic dipeptidase activities (i.e. folate and glutamate or N-acetyl-aspartate, respectively) are thought to be related to multiple cellular processes, such as cell growth, activation of signaling pathways, and DNA repair, which, in

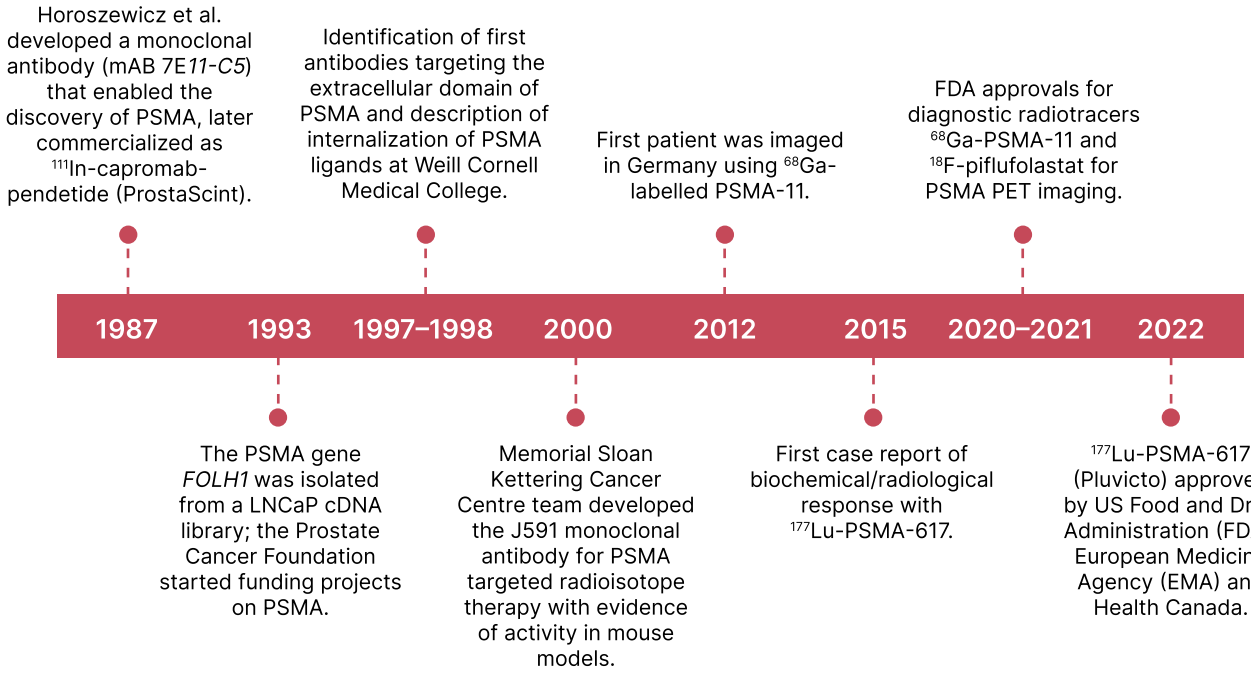

Figure 1. Timeline with key milestones in the development of PSMA theranostics[4,10]; *courtesy of Urban Emmenegger, MD and Rubens Sperandio, MD*

turn, play a role in the proliferation and survival of malignant clones. Moreover, tumoural invasiveness is also being attributed to PSMA activity, as well as contributions to neoangiogenesis in prostate and other cancers.[10]

Importantly, PSMA expression varies across clinical prostate cancer stages. The expression is higher in advanced disease settings, such as metastatic castration-resistant prostate cancer (mCRPC), and in patients with DNA damage repair gene alterations, correlating with poor prognosis and reduced survival. On the contrary, PSMA expression is suppressed in neuroendocrine prostate cancer. Moreover, it is heterogeneously expressed in metastatic sites; for instance, liver metastases tend to express lower levels of PSMA.[11]

In the past decades, PSMA has been a target of interest for diverse therapeutic approaches, including RLT, chimeric antigen receptor (CAR) T-cells, antibody-drug conjugates, and bispecific antibodies and T-cell engagers.

PSMA Diagnostics: How and When to Use

The landscape of PSMA ligands as molecular imaging tools in the diagnostic space is still evolving. The primary techniques utilizing PSMA-binding radiotracers are positron emission tomography (PET) – paired with either computed tomography (CT) or magnetic resonance imaging (MRI) – and single-photon emission computed tomography (SPECT). The use of PSMA PET scans is more widespread than SPECT, and the two agents used mostly are ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (^{18}F-piflufolastat). These tracers are very sensitive and precise in delineating the location of primary tumours, locoregional nodal involvement, and the extent and location of distant metastases in patients with prostate cancer.

PSMA PET imaging has demonstrated higher sensitivity and specificity than conventional cross-sectional imaging (using CT or MRI) and isotope bone scans. While there are differences in the isotope half-lives and practical logistics between each of the PSMA radiotracers, expert panels consider all the approved agents – ^{68}Ga-PSMA-11, ^{18}F-piflufolastat and ^{18}F-rh-PSMA-7.3 (also known as ^{18}F-flotufolastat) – to feature largely equivalent diagnostic characteristics.[12]

There is an ongoing debate in the scientific community regarding replacing conventional with molecular imaging methods, with varying degrees of evidence across the three scenarios described hereafter:

1. *Initial staging:* molecular imaging can guide the feasibility and clinical utility of local therapies, such as radiotherapy or surgical procedures.[13]

2. *Biochemical recurrence:* numerous Phase 3 trials, such as the CONDOR[14] and UCLA/UCSF[15] trials, demonstrated that PSMA-PET imaging is superior to conventional imaging and leads to changes in management in over 60% of cases.[15] Ongoing trials assess whether molecular imaging translates to superior overall survival (OS) and progression-free survival (PFS).
3. *Metastatic setting:* the clinical utility of molecular imaging in the metastatic disease setting (as documented by conventional imaging) is still debatable. Most pivotal clinical trials assessing life-prolonging therapies used conventional imaging for treatment guidance. For this reason, it remains unclear if intensifying treatment for more extensive disease that is only visible by PSMA PET imaging might result in long-term clinical benefit. Moreover, the role of PSMA PET imaging for assessing therapeutic responses is still being determined, with the potential caveat that PSMA is a cell surface antigen and not a biomarker of metabolic activity, as traditionally seen with ^{18}F-fludeoxyglucose (FDG) radiotracers.

Despite its well-documented promise, limited PSMA radiotracer availability/access and costs are barriers and may pose challenges for the widespread incorporation of PSMA diagnostic techniques in many jurisdictions, especially in remote and rural areas. Systems such as PSMA-RADS[16] and PROMISE[17] have been developed and validated with the goal of standardizing the reporting of molecular imaging findings, yet the full implementation of those tools warrants further efforts.

Therapeutic Applications: Impact of PSMA Therapies

Beyond its role in staging and treatment planning, PSMA-targeting has been explored as a vehicle for delivering potent anticancer therapies, notably in more advanced disease settings. RLT has quickly become the forerunner of this approach, by using PSMA's overexpression as a gateway to target radiotherapy to tumoural clusters. Naturally, for this approach to be effective, patients must be selected based on PSMA positivity criteria, and in this respect, trials have varied in the eligibility criteria applied **(Table 1)**. PSMA-negative lesions are commonly defined as metastatic disease with no PSMA uptake in bone lesions with a soft tissue component of ≥1 cm, lymph nodes ≥2.5 cm in the short axis, and visceral metastases of ≥1 cm in size.[18] Intra- and inter-metastatic heterogeneity of PSMA expression, which may also vary over time, is posed as a contributor to resistance to PSMA RLT.

^{177}Lu-PSMA-617 is the most developed PSMA RLT at the moment. This beta-emitting PSMA-radioligand has been approved for use in patients with mCRPC after AR pathway inhibitor (ARPI) and taxane therapy in many countries. It delivers radiation to both PSMA-expressing cells and the surrounding microenvironment within a 0.62 mm range, with a radionuclide half-life of 6.6 days.[19] The radiation effects lead to single-strand DNA breaks, resulting in eventual cell death. Several early-phase trials showed activity and promising response rates in patients with advanced prostate cancer. Given the relatively long half-life of ^{177}Lu, appropriate radiation safety precautions are recommended to minimize exposure to nuclear medicine personnel, family members, and the public. There is emerging evidence that the degree of PSMA expression may correlate with treatment response. **Table 1** summarizes nuances and differences of seminal PSMA-targeted RLT trials, including the TheraP[20], VISION[21], PSMAfore[22], and SPLASH trials.

TheraP is a randomized Phase 2 trial conducted in 11 Australian centres, involving 200 heavily pretreated patients with mCRPC post-docetaxel, randomized 1:1 between ^{177}Lu-PSMA-617 and cabazitaxel. This trial showed a greater prostate-specific antigen (PSA) response of ^{177}Lu-PSMA-617 with radiological PFS (rPFS) benefit with a hazard ratio of 0.63 (95% confidence interval [CI]: 0.46-0.86, p = 0.0028).

VISION is a multicentre, international phase 3 trial that enrolled patients with mCRPC who were pretreated with at least one line of ARPI and one line of taxane chemotherapy. It randomized patients with PSMA-positive lesions in a 2:1 fashion to standard-of-care therapy with or without ^{177}Lu-PSMA-617. The primary endpoint, median rPFS, was longer in the intervention arm, at 8.7 months, compared to 3.4 months in the standard of care arm, with a hazard ratio of 0.40 (95% CI: 0.29-0.75, p < 0.001). Median OS was an alternate primary endpoint, which was also longer for the intervention arm (15.3 vs.11.3 months) with a hazard ratio of 0.62 (95% CI: 0.52-0.74, p < 0.001).

Overall, treatment with ^{177}Lu-PSMA-617 is associated with improved OS, PFS, and quality of life measures, whereas side effects related to

Trial	TheraP	VISION	PSMAfore	SPLASH
NCT Identifier	NCT03392428	NCT03511664	NCT04689828	NCT04647526
Sample size (n)	200	831	468	412
Phase	2	3	3	3
Comparator	Cabazitaxel	Standard-of-care therapy alone (excluded Ra233, chemotherapy, immunotherapy, and other investigational agents)	ARPI change	ARPI change
Randomization	1 to 1	2 to 1	1 to 1	2 to 1
Scenario (ie, prior therapies)	post ARPI and chemotherapy	post ARPI and 1-2 lines of taxane chemotherapy	post one ARPI, chemotherapy-naïve (except [neo]adjuvant ≥ 12 months ago)	post one ARPI, not eligible for or refusing chemotherapy
Selection criteria	^{68}Ga-PSMA-11 PET CT with SUVmax ≥20 in at least ≥1 disease site and >10 at all other metastatic disease sites, and no discordant FDG PET-positive lesions	^{68}Ga-PSMA-11 PET CT with lesion uptake greater than liver parenchyma at ≥1 disease site(s) and no PSMA-negative metastatic lesions	^{68}Ga-PSMA-11 with lesion uptake greater than liver parenchyma at ≥1 disease site and no PSMA-negative metastatic lesions	PSMA-PET scan (i.e., ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL) positive disease as determined by the sponsor's central reader
Dosing	^{177}Lu-PSMA-617: 8.5 GBq initially, reduced by 0.5 GBq per cycle, q6w, up to 6 cycles	^{177}Lu-PSMA-617: 7.5GBq q6w x 4-6 cycles (extended if evidence of response and residual disease) + standard of care therapy	7.4 GBq ± 10% q6w x 6 cycles	^{177}Lu-PNT2002: 6.8 GBq ± 10% q8w x 4 cycles
Primary endpoint(s)	PSA response rate	rPFS, OS (alternate)	rPFS by BICR	rPFS by BICR
PSA50	66%	46%	57.6%	N/A
ORR RECIST	49%	51%	50.7%	N/A

Trial	TheraP	VISION	PSMAfore	SPLASH
Median rPFS	5.1. months versus 5.1 months (HR 0.63, 95% CI 0.46-0.86, p=0.0028)	8.7 months versus 3.4 months (HR 0.40, 95% CI 0.29-0.57, p<0.001)	12.02 months versus 5.59 months (HR 0.41, 95% CI 0.29-0.56, p<0.0001)	9.5 months versus 6.0 months (HR 0.71; p=0.0088)
Median OS	19.1 months vs 19.6 months (restricted mean survival time; p=0·77)	15.3 months versus 11.3 months (HR 0.62, 95% CI 0.52-0.74, p<0.001)	23.66 months versus 23.85 months (HR 0.98, 95% CI 0.79-1.27, p=N/A)	N/A (HR 1.11)
Comments			84.2% crossover rate	84% crossover rate

Table 1. Seminal PSMA-targeted radioligand therapy trials; *courtesy of Urban Emmenegger, MD and Rubens Sperandio, MD*

Abbreviations: ARPI: androgen receptor pathway inhibitor; **BICR:** blinded independent central review; **CI:** confidence interval; **CT:** computed tomography; **FDG:** ^{18}F-fludeoxyglucose; **HR:** hazard ratio; **N/A:** not available; **ORR:** overall response rate; **OS:** overall survival; **PET:** positron emission tomography; **PSA:** prostate-specific antigen; PSA50: 50% or higher PSA response; **PSMA:** prostate-specific membrane antigen; **RECIST:** Response Evaluation Criteria in Solid Tumours**; RLT:** radioligand therapy; **rPFS:** radiological progression-free survival; **SUV:** standardized uptake value.

^{177}Lu-PSMA-617 are typically mild and manageable. Side effects include myelosuppression, gastrointestinal symptoms, such as nausea, xerostomia due to the expression of PSMA in salivary glands, and deteriorating renal function. The current development of PSMA RLT involves the study of such agents in earlier disease stages, such as chemotherapy-naïve mCRPC (PSMAfore, SPLASH) and metastatic castration-sensitive prostate cancer (PSMAddition).

Future of PSMA-targeted Therapies

The use of PSMA RLT does not come without challenges, including limited access or lack of public funding to date in many jurisdictions. Furthermore, inherent therapeutic resistance is not uncommon, and acquired resistance is the typical ultimate outcome. Hence, diverse strategies are exploring ways of improving patient outcomes.[23] Radioligands are being refined in order to improve affinity and decrease toxicity. Using radionuclides other than ^{177}Lu, such as the alpha emitter ^{225}Ac, has shown promising results in retrospective studies, including in ^{177}Lu-resistant cases. Combination strategies to overcome therapeutic resistance are being evaluated in many clinical trials testing poly (ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, and the concurrent use of ARPI amongst others.

Conclusion

In conclusion, PSMA theranostics represent a paradigm shift in the management of prostate cancer, offering both diagnostic precision and therapeutic efficacy. As we continue to unravel the full potential of PSMA-targeted approaches, the future holds great promise for further advancements toward personalized prostate cancer care.

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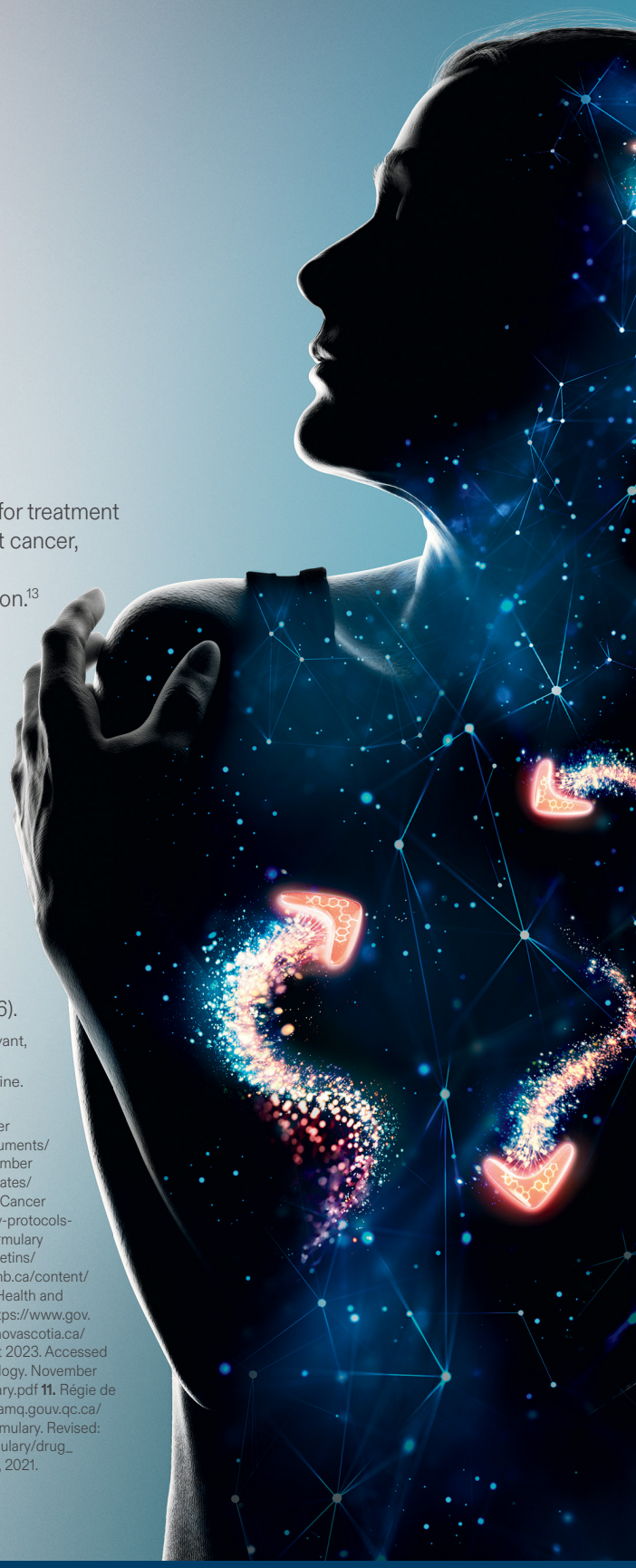

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*The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.[13]

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

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Breast Cancer Survivorship

Nancy Nixon, MD, FRCPC
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Introduction

Breast cancer remains the most common type of cancer among Canadian women, with 28,900 new cases in 2022 alone. Improved detection through screening mammography and advances in multi-modality therapy account for the decline in breast cancer mortality seen in Canada since the 1980s. As 5-year survival rates reach 89%, the number of breast cancer survivors is rising.[1]

The concept of cancer survivorship has existed for decades, as has the appreciation that it is a complex domain of cancer care that begins at the time of diagnosis. Even within the group of patients with breast cancer, survivorship experiences and care needs are diverse, reflecting variability in tumour clinicopathologic characteristics, treatment plans, and prognosis. Evidence-based tools and guidelines suggest the assessment and management of cancer survivor's physical, psychological, social, financial, and employment well-being. There is a need to clinically monitor for breast cancer recurrence and the development of secondary malignancies through screening. Survivorship also warrants attention to health promotion, including weight management, nutrition, physical activity, preventive health, and cessation of alcohol and cigarettes. The provision of survivorship care is the responsibility of all healthcare professionals, which requires close coordination between primary care and specialized cancer centres.[2-4]

In this article, we focus on the physical and psychosocial long-term and late effects faced by survivors of early-stage breast cancer. Many adjuvant therapies for breast cancer are associated with toxicities that negatively impact quality of life (QoL) and adherence. Nonadherence is important to address because it compromises breast cancer outcomes.[4,5]

Long-term and Late Effects Impacting Breast Cancer Survivors

By definition, long-term effects develop during treatment, and late effects develop after completion. Both can persist for years and may include cognitive dysfunction, psychological distress, pulmonary fibrosis, hepatic steatosis, venous thromboembolism, musculoskeletal symptoms, fatigue, osteoporosis, cardiotoxicity, lymphedema, sexual dysfunction, infertility, elevated risk of secondary malignancy, pain, and peripheral neuropathy. Survivors may be left physically and functionally limited after treatment.[3] The risk of physical and psychosocial long-term and late effects in those treated for early-stage breast cancer relates to receptor status, locoregional nodal involvement, genetic predisposition, type of local and systemic treatment strategies employed, duration and dose of therapy, patient age at diagnosis, sex, co-morbidities, and socioeconomic and lifestyle factors.[2-4] In early-stage breast cancer, local therapy is provided with curative intent. Patients typically undergo surgery (breast-conserving or mastectomy with or without axillary lymph node dissection), with or without radiation, and/or reconstruction (immediate or delayed). When patients have an underlying genetic predisposition, specifically in the breast and ovarian susceptibility genes *BRCA1/2*, surgery may involve the contralateral breast, ovaries, and fallopian tubes. Decisions regarding systemic therapy are more nuanced. A combination of endocrine therapy, chemotherapy, biologics, and/or targeted agents may be employed before surgery (neoadjuvant) or after surgery (adjuvant).[2] **Table 1** summarizes systemic therapies available for early-stage breast cancer.[3,6]

Assessment for long-term and late effects should begin at diagnosis but certainly upon treatment initiation as endorsed by national and international evidence-based tools and guidelines, including the College of Family Physicians of Canada (CFPC), European Society of Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO).[2-4] When possible, effects should be anticipated and prevented. Symptoms and signs should be clinically assessed using standardized instruments. Management strategies should incorporate early education, self-management techniques, and pharmacologic and non-pharmacologic interventions. Co-morbidities and polypharmacy, particularly prevalent in older adults (>60 years), who account for most breast cancer cases, should be addressed as they impact long-term and late effects.[1,4]

Below, we discuss the long-term and late effects on neuropsychiatric, bone, reproductive, and sexual health in breast cancer survivors. We focused on these effects due to their high prevalence.

Neuropsychiatric Health

At the time of diagnosis, up to 1 in 4 patients with breast cancer experience some degree of cognitive impairment. This figure rises to 1 in 3 during and for up to 10 years after chemotherapy in breast cancer survivors.[2,7,8] Although chemotherapy has the greatest association with cognitive decline, correlations have also been described for surgery, anaesthesia, radiation, and endocrine therapy.[2] Cognitive decline secondary to treatment is hard to quantify. Studies evaluating this have marked heterogeneity in methodologies, assessment parameters, and time periods of interest. Patient characteristics, including age, menopausal status, education level, and IQ, add further complexity.[2,8]

Cognitive domains impacted by breast cancer and its treatment are broad ranging, including concentration, executive function, memory (particularly short-term), visuospatial awareness, language, and motor functioning.[7] Impact ranges from subtle to severe, causing distress and impaired QoL, which disrupts social, relationship, employment, and financial well-being.[2,3]

Assessments for cognitive impairment include patient self-reporting, short cognitive screening tools, and standardized neuropsychological tests. Patient self-reporting is subjective and results in higher prevalence rates. However, although perceived cognitive problems may not impair performance on objective cognitive assessments, their validity should not be questioned. Unvalidated concerns leave patients disempowered and unsupported with poorer QoL.[8] When cognitive impairment is identified, objectively or subjectively, reversible contributing factors, including fatigue, pain, insomnia, anxiety, depression, and/or menopause-related hormonal changes should be assessed.[2,7,8]

What to do when cognitive impairment is identified in a survivor of breast cancer is less clear. Advice from the ASCO is to refer the patient for formal neurocognitive assessment and rehabilitation, including, where available,

Class of therapy	Treatment indication	Notable long-term and late effects
Chemotherapy	Higher recurrence risk relating to clinicopathologic features and/or gene expression profile testing	**Generic effects:** • Cognitive impairment • Peripheral neuropathy • Osteoporosis • Premature ovarian failure and infertility • Increased risk of second malignancy
Anthracycline-based	Higher-risk breast cancer relating to triple-negative disease, and axillary node positivity in HR+ disease.	• Cardiotoxicity, including heart failure, myocardial infarction, and arrhythmias
Non-anthracycline-based	Where anthracycline-based therapy is not indicated or contraindicated e.g., pre-existing cardiac co-morbidity	• General chemotherapy effects
Endocrine therapy	HR+ disease	**Generic effects:** • Vasomotor symptoms (hot flashes) • Genitourinary changes of menopause (vaginal dryness and atrophy)
Tamoxifen	Pre-menopausal women	• Hepatic steatosis • Venous thromboembolism • Increased risk of secondary malignancy, specifically endometrial cancer
Aromatase inhibitors	Pre-menopausal women undergoing medical (GnRH agonist) or surgical (oophorectomy) OFS Post-menopausal women	• Musculoskeletal symptoms • Osteoporosis
GnRH agonists	Pre-menopausal women requiring OFS due to higher recurrence risk relating to clinicopathologic features and/or gene expression profile testing	• Cardiotoxicity relating to hypertension and dyslipidemia • Osteoporosis
CDK4/6 inhibitors	HR+ disease with higher recurrence risk relating to tumour size, axillary node positivity, grade, and/or Ki67 score	• Gastrointestinal toxicity, specifically chronic diarrhea • Fatigue • Bone marrow suppression • Musculoskeletal symptoms

Class of therapy	Treatment indication	Notable long-term and late effects
PARP inhibitors	Germline BRCA1/2 mutation with higher recurrence risk relating to receptor status, tumour size, axillary node positivity, and/or residual disease post neoadjuvant systemic therapy	• Fatigue • Bone marrow suppression • Increased risk of secondary malignancy, specifically acute myeloid leukemia and myelodysplastic syndrome
HER2-directed therapy	HER2+ disease	
Trastuzumab		• Cardiotoxicity, including heart failure, myocardial infarction, and arrhythmias
Pertuzumab		• Cardiotoxicity, including heart failure, myocardial infarction, and arrhythmias • Gastrointestinal toxicity, specifically chronic diarrhea
Neratinib		• Gastrointestinal toxicity, specifically chronic diarrhea • Fatigue
Bone-modifying agents	Post-menopausal women (including pre-menopausal women receiving OFS), especially if at higher recurrence risk	Generic effects: • Atypical femur fractures • Osteonecrosis of the jaw • Hypocalcaemia
Bisphosphonates		• Nephrotoxicity
Denosumab		• Generic bone-modifying agent effects

Table 1. Systemic therapies available for early-stage breast cancer and their notable long-term and late effects.[3,6]; *courtesy of Nancy Nixon, MD, FRCPC*
Abbreviations: CDK: cyclin-dependent kinase; **GnRH:** gonadotropin releasing hormone; **HER2:** human epidermal growth factor receptor 2; **HR:** hormone receptor; **OFS:** ovarian function suppression; **PARP:** poly (ADP-ribose) polymerase.

group cognitive training. There is inconsistent data to support pharmacologic therapy with modafinil, a non-amphetamine central nervous system stimulant. However, prescribers should be aware that these are associated with several cardiovascular and psychiatric adverse effects.[2]

A diagnosis of breast cancer is distressing, and survivors are at a higher risk of adverse mental health outcomes compared to women without cancer. Adverse mental health outcomes include depression, anxiety, and suicide.[9] Up to 1 in 5 survivors of breast cancer may be affected for years after diagnosis. Reasons for adverse mental health outcomes are complex, including morbidity from other long-term and late effects, difficulties reintegrating into social, intimate, and professional relationships, and uncertainty about the future. Fear of recurrence is a significant cause of distress, depression, and anxiety. This fear may be heightened in those with a higher symptom burden, shorter interval of time since diagnosis, and receipt of chemotherapy.[2] Breast cancer survivorship may also be associated with a higher risk of post-traumatic stress disorder,

Long-term and late effects	Contributing therapies	Assessment	Management
Neuropsychiatric health			
Cognitive impairment	Greatest body of evidence is for chemotherapy, but links are also reported with surgery, radiation, and endocrine therapy	**Subjective:** patient self-reporting **Objective:** short cognitive screening tools and neuropsychological tests When cognitive impairment is subjectively or objectively identified; assess and address reversible contributing factors	**Pharmacologic:** Inconsistent data for modafinil **Non-pharmacologic:** Neurocognitive rehabilitation, including group cognitive training
Distress, depression, and anxiety	N/A	**Distress:** distress thermometer, Depression: Patient Health Questionnaire-9 **Anxiety:** Generalized Anxiety Disorder 7-item scale If depression is identified, screen for suicidal ideation	**Pharmacologic:** Anti-depressants and anxiolytics as per general population but avoid SSRIs in patients on tamoxifen **Non-pharmacologic:** psychotherapy
Bone health			
Osteoporosis & fractures	Endocrine therapy, particularly AIs +/- OFS	• Screen for additional risk factors • Baseline DEXA in pre- and post-menopausal women receiving AI and thereafter every 2 years on therapy	• Lifestyle modification, including daily calcium and vitamin D intake to prevent bone loss • Bone-modifying agents if osteoporosis is diagnosed
Reproductive and sexual health			
Infertility	Chemotherapy, particularly alkylating agents, platinum-based and taxanes Endocrine therapy pauses reproductive plans	Discuss FP and referral to reproductive specialists at outset of breast cancer diagnosis in women of childbearing age Discuss interrupting therapy to try and conceive with primary oncologist	Ovarian and/or embryo cryopreservation is the standard of care Alternative FP techniques include ovarian tissue cryopreservation and ovarian hormone suppression
Genitourinary syndrome of menopause	Endocrine therapy	Screen for symptoms, including vaginal dryness, itching, recurrent UTIs and dyspareunia	Patient education on avoiding irritants, regular use of non-hormonal vaginal moisturizers with non-hormonal lubrication prior to sexual intercourse

Table 2. Assessment and management of key long-term and late effects in breast cancer survivorship; *courtesy of Nancy Nixon, MD, FRCPC*
Abbreviations: AI: aromatase inhibitor; **DEXA:** dual-energy X-ray absorptiometry; **FP:** fertility preservation; **OFS:** ovarian function suppression; **SSRIs:** selective serotonin reuptake inhibitors; **UTIs:** urinary tract infections

somatization, bipolar affective disorder, and obsessive-compulsive disorder. However, these outcomes are studied less frequently, and therefore, the level of evidence for these outcomes is lower.[9]

The distress thermometer, patient health questionnaire-9, and generalized anxiety disorder 7-item scale screen for distress, depression, and anxiety, respectively. A more thorough assessment should be employed for those patients who are known to be at the highest risk, including patients who are young, have psychiatric co-morbidities, are of low socioeconomic status, and/or are unemployed. When elevated scores are identified, further assessment and management is warranted. Patients with depression should always be screened for suicidal ideation.[2]

Breast cancer survivors experiencing adverse mental health outcomes should be referred to mental health professionals and/or psychosocial oncology specialists based on the local resources available. Pharmacologic strategies, including anti-depressants and anxiolytics, as employed in the general population, are appropriate, except for selective serotonin reuptake inhibitors in women on tamoxifen, as efficacy is impaired in this group.[3] Non-pharmacologic strategies also play an important role and include psychotherapy, mindfulness, expression of positive emotions, spiritual interventions, hope therapy, and meaning-making interventions.[2]

Bone Health

Bone loss occurs progressively in women with age. Driven by estrogen deficiency, bone loss is most marked post-menopause. Endocrine therapy expedites the rate and magnitude of bone loss, reducing bone mineral density (BMD) and increasing fracture risk, even upon treatment discontinuation.[10] Concomitant risk factors, including a personal or family history of fractures, low physical activity, excess alcohol use, and smoking, may exacerbate effects.[2] BMD loss is highest (up to 11% per year), in pre-menopausal women receiving aromatase inhibitors (AIs) with ovarian function suppression (OFS). Even women receiving tamoxifen, considered to have anti-resorptive properties, lose up to 2% of their BMD annually.[11] Loss of BMD should also be considered in pre-menopausal women at risk of premature ovarian failure with chemotherapy and where glucocorticoids are used.[2] In post-menopausal women in whom OFS is not required, bone loss and fracture risk are most pronounced with the use of AIs. Extending AI therapy beyond five years increases the fracture risk further and is an important consideration.[10]

Strategies to prevent bone loss should be considered at diagnosis. Although evidence is limited, lifestyle modifications, including physical activity, weight-bearing exercises, and cessation of smoking and alcohol, should be advised. Daily intake of vitamin D (600-1000 IU) and calcium (1200 mg) should be encouraged, and supplementation should be considered.[2] Osteoporosis Canada provides guidance on assessment of bone health in patients with breast cancer who are using endocrine therapy, which they recognize as a high-risk medication. Post-menopausal women should be screened with a baseline DEXA scan upon AI initiation, which should be repeated every two years while on therapy. This is also warranted in premenopausal women receiving AI with OFS.[12]

Select post-menopausal patients with early-stage breast cancer receive adjuvant bone-modifying agents to reduce recurrence risk and improve mortality, as outlined in **Table 2**. Beyond this context, bone-modifying agents, including bisphosphonates and denosumab, are largely reserved for osteoporosis treatment. These are not routinely used for prevention, given their risks of atypical femur fractures, jaw osteonecrosis, and, in the case of denosumab, rebound osteolysis.[2,10]

Reproductive and Sexual Health

Breast cancer is the most common malignancy diagnosed in Canadian women of childbearing age.[1] Many of the systemic therapies employed compromise fertility and reproductive hopes. This detrimentally impacts the well-being of breast cancer survivors. Chemotherapy, particularly alkylating agents, platinum-based chemotherapy, and taxanes, are gonadotoxic, resulting in premature ovarian insufficiency and infertility. Endocrine agents, although not gonadotoxic per se, require women with hormone receptor-positive (HR+) breast cancer to pause reproductive plans for the 5-10 years they are on treatment. Less is known about whether and how HER2-directed therapies, poly (ADP-ribose) polymerase (PARP) inhibitors, and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors impact fertility. While biological parenthood is possible for young breast cancer survivors, it requires pretreatment planning and intervention.

Thus, at the time of breast cancer diagnosis, fertility preservation (FP) should be discussed, and a referral made to reproductive specialists, even in patients who express ambivalence towards reproduction.[10,13] We recognize, however, that the lack of financial resources remains a significant barrier to access because FP is not publicly funded in Canada.

Assisted reproductive technologies (ART) with either oocyte and/or embryo cryopreservation remains the standard of care for FP in patients with breast cancer before starting therapy. Therapeutic advances mean ART can be started at any time during the menstrual cycle, minimizing treatment delays. Simplistically, gonadotropins stimulate the ovaries to produce multiple mature oocytes, which are then retrieved and fertilized to produce embryos, in cases where sperm is available. In HR+ breast cancer, in which high levels of estradiol should be avoided, ovarian stimulation is performed with AIs or tamoxifen. This reduces circulating estradiol without affecting the number of oocytes retrieved, their maturation, or fertilization.[10,13] Ovarian stimulation is safe in breast cancer and does not compromise recurrence or survival, even in HR+ disease.[14]

Alternative FP options are available, including ovarian tissue cryopreservation and ovarian hormone preservation. Ovarian tissue cryopreservation can be performed immediately and does not require stimulation. Once considered experimental, it can achieve live birth rates of ~60%; however, anaesthesia, these data are based on patients with and without cancer.[15] Ovarian hormone preservation involves concurrent administration of chemotherapy with gonadotropin receptor hormone agonists (GnRHa). The ovaries are suppressed by GnRHa, protecting them from the gonadotoxic effects of chemotherapy. Data supporting GnRHa use is largely obtained from women with other causes of premature ovarian failure and aim to reduce long-term risks to bone and cardiovascular health. There is some data that use in breast cancer reduces the risk of premature ovarian failure and improves pregnancy rates, but the evidence is limited. ASCO continues to advise that it should not be used instead of proven FP methods.[13,16]

Although we recognize that pregnancy and trying to conceive are important considerations for young breast cancer survivors, discussing the likelihood of this, reproductive outcomes, and maternal safety is beyond this article's scope. However, we emphasize that young breast cancer survivors can become pregnant, but close consultation with the patient's primary oncologist is needed. Many of our systemic therapies are teratogenic, and washouts are required. There is clear guidance on chemotherapy (12 months), trastuzumab (7 months), and tamoxifen (3 months) use, but less information is available for pertuzumab, CDK4/6 inhibitors, and PARP inhibitors.[17] Regarding endocrine therapy, the POSITIVE landmark study showed that treatment interruptions for up to 2 years, during which young women can try to conceive, did not worsen short-term breast cancer outcomes (breast cancer-free interval and distant relapse-free survival). Given the natural history of HR+ breast cancer, in which delayed recurrences occur, long-term follow-up is needed to safely determine if and how treatment interruptions impact relapse rates and survival.[18]

Genitourinary syndrome of menopause (GSM) also compromises breast cancer survivors' sexual health. Largely related to endocrine therapy, it is also observed in women with premature ovarian insufficiency post-chemotherapy. GSM is caused by estrogen suppression to levels below that naturally expected post-menopause. Vaginal and vulval atrophy secondary to hypoestrogenism results in dryness, which can itch and burn, with increased risks of urinary tract infections and dyspareunia. Left untreated, vaginal stenosis and shortening may develop. The detrimental impact of GSM on survivor well-being cannot be understated and is an important cause of treatment nonadherence.[10]

Patient education is vital for managing GSM, as simple strategies can help. Irritants, including feminine washes, alcohol-based wipes, and topical agents containing artificial fragrances, parabens, petroleum, propylene glycol, and glycerin, should be avoided. Non-hormonal moisturizers and lubricants should be recommended, recognizing that patients often require clarification on their differential use. Non-hormonal moisturizers are for regular use, with application to the vaginal and vulval mucosa at least three times per week. Simple emollients, including coconut oil, may suffice, but hyaluronic acid-containing agents are also helpful. Consistent use is key for beneficial effects. Prior to sexual intercourse, non-hormonal lubricants should be applied. Silicone-based lubricants are preferred, but water-based versions are also acceptable. Should dyspareunia remain problematic, consider vaginal stenosis and shortening. If found on physical examination, pelvic floor physical therapy and use of a vaginal

dilator at least three times a week should be encouraged. Again, consistency is key. The role of hormonal moisturizers, specifically estradiol or dehydroepiandrosterone preparations, remains a source of ongoing debate, given apprehension regarding systemic absorption. Concern was recently renewed based on published data suggesting increased recurrence risk when used in women with HR+ breast cancer.[19] Proposed harmful effects of topical hormonal therapy should be balanced against increased recurrence risk secondary to endocrine therapy nonadherence. Careful counselling is warranted for women in whom non-hormonal strategies have failed, and hormonal moisturizers are being considered.[10]

Although GSM contributes to sexual dysfunction and disrupted sexual intimacy in breast cancer survivors, further complexities exist that relate to decreased libido, arousal concerns, loss of sexual sensitivity of the skin, and orgasmic concerns that do not just affect women on endocrine therapy. Chemotherapy, surgery, and radiation all contribute, and many breast cancer survivors are affected. Referral for interventions, including psychoeducational support, group therapy, intensive psychotherapy, and sexual and/or marital counselling, are advised by ASCO.[2]

Treatment Adherence

Assessment and management of long-term and late effects is crucial because it influences treatment adherence. In early-stage breast cancer, compliance is particularly problematic with adjuvant endocrine therapy, despite its value in recurrence rate reduction (~1/2 in the first 10 years) and survival improvement (1/3 in the first 15 years) in HR+ disease.[20] A third of patients receiving endocrine therapy are nonadherent. Further, adherence decreases over time, on average by ~25% from year 1 to 5. Although these reductions in adherence are observed with all endocrine agents, nonadherence is higher with tamoxifen than AIs. Thus, pre-menopausal breast cancer survivors are impacted most.[21]

Nonadherence is difficult to quantify. Clinicians often rely on patient self-reporting, a measure consistently proven to overestimate adherence. In a prospective study measuring serum detection of tamoxifen in approximately 1,200 pre-menopausal women, biochemical nonadherence at 1 year was 16%. Even at a median follow-up of only two years, this subgroup had comparatively inferior breast cancer-specific outcomes independent of other prognostic factors.[5] Many pre-menopausal women additionally receive OFS, which increases toxicity. The addition to tamoxifen increases vasomotor symptoms, while the addition to AIs increases impairments in musculoskeletal and sexual health. How this increase in toxicity contributes to treatment nonadherence remains unclear. Certainly, within the landmark SOFT/TEXT clinical trials, early treatment discontinuation was ~20% in patients across all three treatment groups, namely: tamoxifen alone, tamoxifen with OFS, and exemestane (AI) with OFS.[22]

The treatment landscape of early-stage breast cancer is evolving. Notably, two to three years of CDK4/6 inhibition is combined with adjuvant endocrine therapy in HR+ disease. Although currently only approved by Health Canada for patients with a pre-defined higher recurrence risk, access may broaden in years to come. In the monarchE trial, the addition of abemaciclib (CDK4/6 inhibitor) to endocrine therapy increased grade ≥3 adverse effects and treatment discontinuation.[23] Despite treatment evolution, benefits in breast cancer-specific outcomes will not be gained in real-world clinical practice if patients remain nonadherent because of long-term and late effects.

Conclusion

As 5-year breast cancer survival rates reach 89%, now more than ever, healthcare providers have an obligation to recognize the experiences and care needs of survivors. Survivorship is a complex domain of cancer care that starts at the time of diagnosis. It encompasses assessment for disease recurrence, screening of secondary malignancies, health promotion, and management of both long-term and late effects of treatments received. Long-term and late effects impair QoL and contribute to treatment nonadherence and are, therefore, crucial to address.

Cognitive impairment predates a breast cancer diagnosis in 1 in 4 patients. This can worsen during treatment and last many years after. Although patients self-report cognitive impairment post-therapy at higher rates than that detected through objective measures, validity should not be questioned as this disempowers the patient and compromises QoL. Breast cancer survivors are at greater risk of adverse mental health outcomes than those without cancer. This

includes distress, depression, anxiety, and suicide. Validated screening tools are available and should be employed to ensure patients will receive the pharmacologic and non-pharmacologic therapies needed.

Bone health is markedly compromised by endocrine therapy, which increases the rate and magnitude of BMD loss, increasing fracture risk. Risk is greatest with AIs, and prescribers should be particularly mindful when co-administering with OFS, and consider treatment extension beyond five years. Evidence for lifestyle modification strategies is limited but should be encouraged to prevent BMD. Bone-modifying agents should only be used to treat (not prevent) osteoporosis, as this therapy can also disrupt bone health.

Chemotherapy is gonadotoxic, and endocrine therapy disrupts reproductive plans for years while on treatment. Breast cancer is the most common malignancy diagnosed in women of childbearing age, and FP should be discussed before treatment initiation. Referral to reproductive specialists should be made, even when patients are ambivalent, recognizing that in Canada, financial limitations are a barrier to pursue FP. It is important not to underestimate the impact of GSM on sexual dysfunction. Ask patients if they are symptomatic, and inform them there are simple strategies that, with consistent use, can prove effective.

Long-term and late effects contribute to treatment nonadherence. This is particularly important with endocrine therapy, because despite solid evidence supporting reductions in recurrence risk and improved survival, many patients do not comply. Nonadherence increases over time. Although there is currently no evidence to suggest nonadherence increases with the addition of OFS, the addition of CKD4/6 inhibition has been shown to increase treatment discontinuation. Therapeutic advances will not lead to improved breast cancer-specific outcomes in real-world practice unless long-term toxicities are assessed and addressed, as is crucial for effective survivorship care.

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Tailored Approaches and Patient-centered Care: The Current Landscape of Neoadjuvant Therapy in Rectal Cancer

Tharani Krishnan, MD

Introduction

Colorectal cancer (CRC) is the third most diagnosed cancer in Canada and worldwide.[1] Although mortality rates have declined, it remains the second most lethal malignancy worldwide.

For patients with locally advanced rectal cancer (LARC), several new concepts have been introduced in recent years for treatment sequencing and de-escalation. The use of pelvic magnetic resonance imaging (MRI) for initial staging and neoadjuvant therapy response assessment has become a key part of the workup for LARC, utilizing the expertise of specialist radiologists. High-volume rectal cancer centers have adopted total neoadjuvant therapy (TNT) as a preferred approach for many patients with LARC. There is rising interest in shortening the duration of chemotherapy or radiation, or even omitting radiation altogether for select patients, to reduce the burden of long-term toxicities. For patients who achieve clinical complete or near-complete responses (cCR or nCR) to neoadjuvant therapies, nonoperative management (NOM) has emerged as an option to avoid the complications of a total mesorectal excision (TME).

This paradigm shift has resulted in numerous treatment options for many patients with rectal cancer, enabling a more individualized, multidisciplinary approach to care.[2] Clinicians must understand how to interpret the evidence around these new concepts to successfully implement them into clinical practice. This review summarizes the recent evidence for neoadjuvant therapy approaches in rectal cancer to provide a context for this paradigm shift to a tailored therapeutic strategy.

Total Neoadjuvant Therapy

Neoadjuvant chemoradiation is the established standard of care for patients with Stage II and III rectal cancer since the results of the German Rectal Cancer Study 20 years ago.[3] However, more recently, there has been a growing interest in moving systemic chemotherapy earlier in the treatment sequence, resulting in the concept

of TNT, whereby all chemotherapy is delivered prior to surgery.

The potential benefits of this shift in treatment sequencing can be divided into those impacting efficacy, safety, and treatment adherence. Evidence from multiple trials shows that TNT results in improved oncologic outcomes compared to standard chemoradiation alone. In the PRODIGE-23 trial, modified oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil (FOLFIRINOX) before preoperative chemoradiation was compared to standard preoperative chemoradiation with adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX).[4] The updated results showed a disease-free survival (DFS) and overall survival (OS) benefit at seven years for the TNT arm.[5] The RAPIDO trial used a slightly different experimental arm of short-course radiation followed by three months of FOLFOX prior to surgery, compared to long-course chemoradiation followed by surgery and optional adjuvant chemotherapy.[6] The most recent results of this trial showed a sustained benefit in the TNT arm for disease-related treatment failure. In this trial, no difference in OS was observed between the two arms, and interestingly, there was a higher rate of locoregional recurrence in the TNT arm compared to long-course chemoradiation.[7] The Phase III TNTCRT trial also differed slightly in its experimental arm, comparing capecitabine and oxaliplatin (CAPOX) TNT to standard long-course chemoradiation and adjuvant chemotherapy **(Table 1)**. This study also showed a significant improvement in DFS for the TNT arm but no difference in OS.[8]

Concerning safety and treatment adherence, multiple studies have shown similar or reduced rates of serious toxicity with a TNT approach.[4,6,8,9] Surgical risk and complication rates do not appear to be significantly worsened with the shift to preoperative chemotherapy compared to standard adjuvant chemotherapy, even with the use of FOLFIRINOX in the PRODIGE-23 trial.[4]

Patient selection is critical to ensure that maximal benefit from TNT is achieved, over-treatment of patients with lower-stage disease is minimized, and unnecessary chemotherapy-related complications are avoided. Where possible, cases should be reviewed in a multidisciplinary tumour board. The specific inclusion criteria for TNT differ between the current trials. For example, in the PRODIGE-23 trial, patients with cT3 or cT4 disease were included. However, the RAPIDO and TNT CRT trials included a more high-risk cohort, including those with cT4a or cT4b tumors, who were extramural vascular invasion (EMVI) positive, in which the mesorectal fascia was involved, or those with a higher nodal burden (cN2 or enlarged lateral nodes).[4,6] Generally speaking, patients should have Stage 3 disease and/or higher-risk features to have maximal benefit from this treatment intensification.

Radiation-sparing Approach

The avoidance of radiation has emerged as a potential option for select patients, with a key driver being the prevention of long-term radiation toxicity. Recent evidence comes from the PROSPECT study, a randomized non-inferiority trial in patients with early- or intermediate-advanced upper and mid rectal cancers.[10] Patients received either standard long-course chemoradiation or three months of FOLFOX with select use of chemoradiation (in cases with <20% tumor response or <5 cycles received due to toxicity) prior to surgery, which is then followed by adjuvant chemotherapy. Only 9% of patients in the experimental arm ultimately required neoadjuvant chemoradiation. The trial met its primary endpoint, confirming the non-inferiority of FOLFOX with selective chemoradiation. Notably, at twelve months after treatment, patients in the experimental arm reported less bowel, bladder, and sexual dysfunction compared to those in the standard chemoradiation arm.

Avoiding radiation has emerged as a useful option for specific patient subgroups, such as young women hoping to preserve fertility. Patient selection is again important, as the PROSPECT study excluded patients with T4 and N2 disease and those with low rectal cancers. Potential future approaches include the expansion of radiation avoidance to patients with early-stage rectal cancers. For example, the currently recruiting Neo-RT trial will explore the role of minimally invasive surgery after neoadjuvant FOLFOX and selective radiation in patients with T1 and T2 rectal cancers.[11]

Neoadjuvant Immune Checkpoint Inhibitor Therapy for Mismatch Repair-deficient Rectal Cancer

Up to 10% of rectal cancers may carry a germline or somatic deficiency in DNA mismatch repair (dMMR) and are less responsive to fluoropyrimidine-based chemotherapy.[12,13] For patients with dMMR advanced CRC, the

Author	Year	Common name	Format	Patients	Clinical stage included	Mandatory TME	Landmark follow-up (years)	Study arms	DFS	OS	pCR (%)
MMR proficient											
Conroy *et al.*[4,5]	2021, 2023	PRODIGE-23	Phase III RCT	461	T3-4	Yes	7	3 mos FOLFIRINOX then LCCRT prior to TME, then 3 mos ACT CRT prior to TME, then 6 mos ACT	66.2% vs. 60.4% [S]	76.3% vs. 71.9% [S]	28% vs. 12% [S]
Bahadoer *et al.*[6,7]	2021	RAPIDO	Phase III RCT	912	At least 1 of: T4a/b, EMVI, N2, involved MRF or lateral LNs	Yes	5	SCRT then 3 mos CAPOX or FOLFOX, prior to TME LCCRT prior to TME, then 4 mos ACT	DrTF 27.8% vs. 34% [S]	81.7% vs. 80.2% [NS]	28% vs. 14% [S]
Wang *et al.*[8]	2024	TNTCRT	Phase III RCT	458	T4, N2, T3c-d with EMVI, threatened MRF	Yes	3	1 cycle CAPOX then 2 cycles CAPOX with concurrent RT, then further 3 cycles CAPOX, prior to TME LCCRT prior to TME, then ACT	76.8% vs. 67.9% [S]	89.8% vs. 88.2% [NS]	27.5% vs. 9.8% [S]
Schrag *et al.*[10]	2023	PROSPECT	Phase III randomized noninferiority	1128	T2N1, T3N0 or T3N1	Yes (sphincter-sparing surgery)	5	3 mos FOLFOX then selective LCCRT prior to TME, option of ACT LCCRT prior to TME, option of ACT	80.8% vs. 78.6%	89.5% vs. 90.2%	21.9% vs. 24.3%

Author	Year	Common name	Format	Patients	Clinical stage included	Mandatory TME	Landmark follow-up (years)	Study arms	DFS	OS	pCR (%)
Verheij *et al.*[19,20]	2024	OPRA	Phase II randomized trial	324	T3-4N0 or N1-2	No	5	INCT-CRT prior to TME or NOM CRT-CNCT prior to TME or NOM	71% and 69%	88% and 85%	TME-free survival 39% and 54%
MMR-deficient											
Cercek *et al.*[15,16]	2022, 2024	Dostarlimab study	Phase II	42	II and III	No	1.5	6 mos dostarlimab then NOM if cCR, or CRT and TME if residual disease	100%	100%	cCR 100%
Chen *et al.*[17]	2023	Sintilimab study	Phase II	16	T3-4 or N+	No	1.5	8 cycles sintilimab before TME or NOM, or 4 cycles sintilimab before TME then 4 cycles adjuvant sintilimab +/- CAPOX	100%	100%	cCR 75%

Table 1. Recent key trials for neoadjuvant therapy in rectal cancer; *courtesy of Tharani Krishnan, MD*
Abbreviations: ACT: adjuvant chemotherapy; **CAPOX:** capecitabine plus oxaliplatin; **cCR:** clinical complete response; **CRT:** chemoradiotherapy; **CRT-CNCT:** chemoradiotherapy followed by consolidation chemotherapy; **DFS:** disease-free survival; **DrTF:** disease-related treatment failure; **EMVI:** extramural vascular invasion; **FOLFIRINOX:** folinic acid, fluorouracil, irinotecan, and oxaliplatin; **FOLFOX:** folinic acid, fluorouracil, and oxaliplatin; **INCT-CRT:** induction chemotherapy followed by chemoradiation; **LCCRT:** long-course chemoradiotherapy; **LNs:** lymph nodes; **MMR:** mismatch repair; **mos:** months; **MRF:** mesorectal fascia; **NOM:** nonoperative management; **OS:** overall survival; **pCR:** pathological complete response; **RCT:** randomized controlled trial; **RT:** radiotherapy; **SCRT:** short-course radiotherapy; **TME:** total mesorectal excision; **vs.:** versus; **[NS]:** not significant; **[S]:** significant.

established standard-of-care first-line treatment is the immune checkpoint inhibitor (ICI) pembrolizumab.[14]

Several prospective studies in patients with early-stage dMMR CRC have recently demonstrated robust responses to ICIs. For patients with dMMR LARC specifically, 6-month treatment with dostarlimab achieved a cCR rate of 100% in a single-arm Phase II study including 42 patients.[15,16] With a median follow-up of 17 months, no patients have required chemoradiation or surgery. Another Phase II study of neoadjuvant sintilimab given for 12 to 24 weeks resulted in a cCR in 12 out of 15 patients.[17] While promising and likely to change practice, larger studies with longer follow-up are awaited to confirm the sustained benefit of neoadjuvant ICIs. Several unanswered questions remain, such as the optimal duration of treatment, the need for combination ICI treatment, and the role of NOM for sustained cure after ICIs. Access to this treatment outside of a clinical trial setting remains an issue in Canada, with ICIs only approved in the first-line dMMR metastatic setting.

Nonoperative Management

Patients with rectal cancer are increasingly interested in pursuing NOM. The purpose of omitting surgery is primarily to allow for organ preservation and minimize the risk of late complications, including urinary incontinence and bowel and sexual dysfunction. This is particularly important for patients with low rectal cancers, who often wish to avoid the permanent ostomy associated with an abdominoperineal resection (APR). In fact, a survey of patients in Canada found that patients would accept a 20% absolute decrease in survival with NOM relative to APR, while physicians would only accept a 5% survival reduction.[18]

While the NOM approach was initially reported for patients who achieved a cCR after chemoradiation alone, TNT has enabled maximal downstaging, and may allow for NOM in up to half of patients with LARC. In a prospective Phase II study, increasing the duration of chemotherapy from zero to three months after chemoradiation resulted in higher pathologic complete response (pCR) rates (18%-38%).[9] Additionally, an intermediate group of patients who achieve nCR after TNT may also benefit from NOM.

In the randomized Phase II OPRA trial, patients received either chemoradiation followed by four months of consolidation chemotherapy (CNCT) or chemoradiation after induction chemotherapy (INCT). Those who achieved a cCR or nCR were offered NOM; otherwise, TME was recommended. 5-year DFS rates were similar between the two arms.[19] However, TME-free survival was 54% in the CNCT arm and 39% in the INCT arm. For those with tumor re-growth, 94% occurred within the first two years. DFS was similar for patients who underwent TME after neoadjuvant therapy and TME after re-growth. The updated analysis shows organ preservation in approximately half of the patients, with higher rates (77%) in those with a cCR compared to nCR (40%).[20]

Accurately assessing clinical tumor response after neoadjuvant therapy is paramount to selecting patients for NOM. In the OPRA trial, patients had biopsy-proven rectal adenocarcinoma, and were staged with pelvic MRI, a full colonoscopy, and computed tomography (CT) of the chest, abdomen, and pelvis. Re-assessment occurred at 8 ± 4 weeks after completion of neoadjuvant therapy, and included digital rectal examination, endoscopy, and MRI. At the initial consultation, baseline features associated with lower cCR rates should be considered, such as tumor <1 mm from the circumferential resection margin, EMVI, and extensive mesorectal/pelvic nodal involvement. In addition, limitations exist with regard to accurately distinguishing post-radiation changes from residual disease and may add complexity to the decision of whether to offer NOM to a patient.

NOM should be undertaken in high-volume centers with experienced MRI radiologists and colorectal surgeons, and ideally in the context of a clinical trial or standardized protocol. Ongoing trials are investigating the optimal algorithms of TNT delivery and response assessment to further expand the number of patients who may benefit from NOM.

Conclusion

The neoadjuvant approach to rectal cancer is an evolving area. Results of several clinical trials in recent years have led to a paradigm shift towards tailoring an individualized treatment sequence that aligns with the patient's goals. Improvements in systemic therapy options, radiation delivery, and surgical expertise can potentially spare patients from adverse long-term treatment sequelae, while maintaining oncologic outcomes. A concerted

multidisciplinary approach should be considered mandatory for developing appropriate patient-centered strategies for patients with LARC.

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Antibody-drug Conjugates in The Management of Advanced Urothelial Carcinoma

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Introduction

For decades, the cornerstone for treatment of advanced urothelial carcinoma (aUC) has consisted of platinum-based chemotherapy regimens, such as GC (gemcitabine plus cisplatin/carboplatin) or MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin).[1] Thereafter, immune checkpoint inhibitors (ICI) were incorporated into the standard of care, initially as monotherapy in subsequent-line settings and more recently as maintenance treatment with chemotherapy in the first-line setting.[2-5] Recently, the development of antibody-drug conjugates (ADCs) has dramatically shifted the treatment landscape for aUC.

ADCs are engineered to function as a biologic *"honing missile"*,[6] with the aim of delivering its cytotoxic payload to the target cancer cell while remaining stable in circulation and minimizing off-target toxicity. Enfortumab vedotin was the first to demonstrate efficacy in urothelial carcinoma (UC),[7] initially as monotherapy and later in combination with ICI, surpassing the decades-old standard of first-line chemotherapy.[8] The aim of this review is to discuss the evolving field of ADCs in aUC, highlighting the main targets, clinical data, toxicities, and future opportunities.

The "ABCs" of ADCs

An ADC is composed of three primary elements: A) a target-specific antibody, B) a cytotoxic payload, and C) a linker molecule that conjugates the two. The antibody's target determines its tissue specificity. Ideally, the target is an antigen preferentially expressed on tumour tissue and minimally expressed on non-malignant tissue to reduce off-target side effects.[9] Moreover, the antibody should have minimal immunogenicity to avoid neutralization and/or hypersensitive reactions from the host's immune system.[10]
In the UC context, ADC research to date has concentrated on targeting three highly expressed cell-surface proteins: nectin-4, trophoblast cell surface antigen-2 (trop-2), and the ErbB family of receptors **(Figure 1)**.

The cytotoxic payloads currently employed in UC are classified into microtubule destabilizers (e.g. auristatins) and topoisomerase inhibitors (e.g. deruxtecan, SN-38). Due to their high potency, these agents are typically unsuitable for direct administration; however, when conjugated to antibodies, they can be delivered systemically with reduced toxicity.[11] The *drug-antibody ratio* (DAR) is the number of cytotoxic molecules bound to each antibody, and higher DARs can increase the efficacy of ADCs.

Linkers maintain the stability of ADCs in systemic circulation and control the payload delivery to target cells. Cleavable linkers facilitate payload release via enzymatic or pH-triggered degradation, delivering the payload to not only target cells but also the surrounding tumour microenvironment, termed the *bystander effect*. While the bystander effect can be beneficial in therapy, cleavable linkers also carry the risk of premature payload release and potential systemic toxicity. In contrast, ADCs with non-cleavable linkers release their payload only after the ADC is internalized and degraded inside the target cell, which can reduce systemic toxicity. This, however, can also increase an ADC's half-life, which may lead to distinct delayed toxicities. Therefore, the engineering of linkers plays a vital role in balancing toxicity and efficacy.[11]

ADCs by target

Nectin 4

Nectin-4 is a transmembrane cell-adhesion molecule expressed at low levels in healthy tissues of the aerodigestive tract, skin, and placenta.[12] Aberrant expression has been observed in several

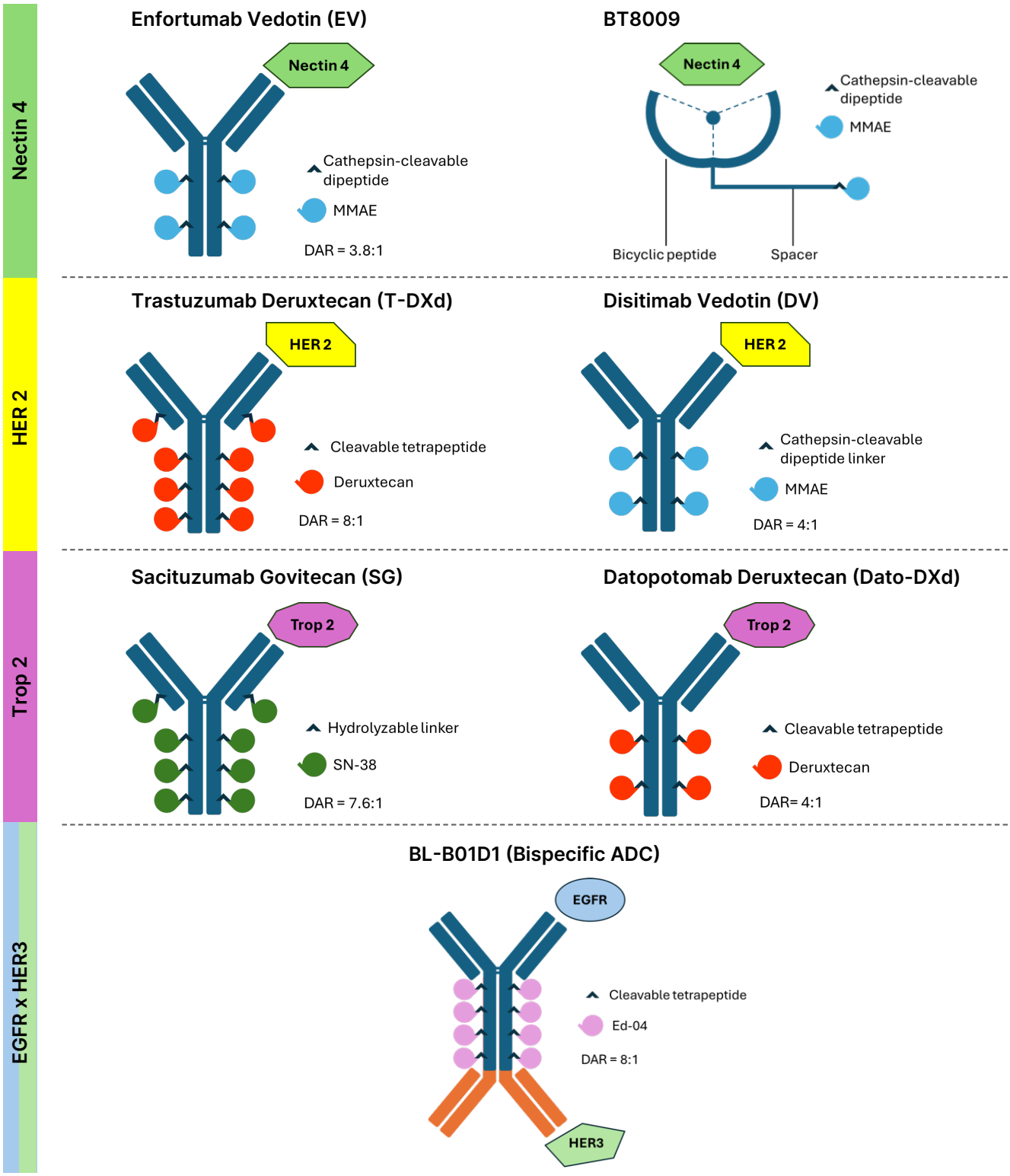

Figure 1. Structures of antibody-drug conjugates (ADC) and a bicycle toxin conjugate (BTC) used in advanced urothelial carcinoma. Each ADC consists of a target-specific antibody, linker molecule, and cytotoxic payload. A BTC uses a small molecule (0.9 kD) bicyclic peptide with a high target-affinity in lieu of an antibody; courtesy of Pooya Dibajnia, BSc (Hons), MD, FRCPC and Aly-Khan Lalani, BSc (Hons), MD, FRCPC; *courtesy of Pooya Dibajnia, BSc (Hons), MD, FRCPC and Aly-Khan Lalani, BSc (Hons), MD, FRCPC*

Abbreviations: DAR: drug-antibody ratio; **EGFR:** epidermal growth factor receptor; **HER2:** human epidermal growth factor receptor 2; **HER3:** human epidermal growth factor receptor 3; **MMAE:** monomethyl auristatin E.

tumour types, including bladder, breast, lung, pancreatic, and ovarian cancer, which makes it an ideal target for engineering ADCs for aUC.[13]

Enfortumab vedotin (EV) is the first nectin-4 targeting ADC, which contains the microtubule destabilizer monomethyl auristatin E (MMAE) as its payload. Two pivotal phase III trials have established the role of EV in the management of aUC. In the subsequent-line setting, the EV-301 trial compared EV versus chemotherapy in patients previously treated with platinum-based chemotherapy and ICI. The EV arm was associated with an improved median overall survival (mOS) of 12.9 months versus 8.9 months (hazard ratio [HR] = 0.70) in the chemotherapy arm.[7, 14] The benefit of EV in platinum-ineligible patients post-ICI therapy has also been demonstrated in the phase II setting.[15] In the first-line setting, the EV-302 trial showcased the efficacy of EV in combination with pembrolizumab (PD-1 inhibitor) compared to platinum-based chemotherapy. This trial with 886 patients demonstrated a significant improvement in mOS of 31.5 months for the EV + pembrolizumab arm versus 16.1 months for the chemotherapy arm (HR = 0.47). The overall response rate (ORR) was 67.7% with EV + pembrolizumab, compared to 44.4% with chemotherapy. These studies have led to the approval of EV by the US Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency **(Table 1)**. The use of EV in the first- and subsequent-line settings is being incorporated into guideline recommendations.[16]

Clinicians need to be mindful of several unique toxicities associated with EV. Peripheral neuropathy can be caused by the neurotoxic payload MMAE. It is observed in 30-40% of patients when EV is used as a single agent,[7, 17, 18] and potentially a higher percentage when combined with pembrolizumab.[8] Sensory neuropathy is the most commonly reported form; however, motor and autonomic neuropathy are also possible. Vigilant monitoring is critical in patients who may carry subclinical neuropathy (e.g. diabetes, older age). High-grade neuropathy, observed in 3-4% of patients, may require dose reductions or discontinuation of therapy. In addition, dermatologic toxicities occur in 30-40% of patients.[18] The presumed mechanism of dermatologic toxicities is on-target/off-tumour binding of EV to normal nectin-4 expressing tissue (e.g. epidermis, hair follicles). This can present in various forms, including maculopapular rash (typically in skin folds), stomatitis, conjunctivitis, and bullous dermatitis.[19] Finally, hyperglycemia is observed in up to 10% of patients, with approximately 6% being grade 3 or higher, necessitating caution in patients with diabetes.[20]

Ongoing studies of other nectin-4-based therapies use various combinations of antibodies, payloads and/or linker molecules.[21, 22] Bicycle toxin conjugates (BTC) are a novel class of therapeutic that have evolved from the design principles of ADCs. BTCs employ a small molecule bicyclic peptide with a high target affinity in lieu of an antibody. The theoretical advantage of BTCs is that the small size allows better infiltration of tumour tissue and improves systemic clearance, thereby improving outcomes and reducing toxicities. BT8009 is a nectin-4-based BTC that has demonstrated an ORR of 50% in early phase trials,[23] and is currently being explored in the phase II/III Duravelo-2 trial for aUC **(Table 1)**.[24]

ErbB family

The ErbB family of cell-surface receptors are highly expressed in urothelial carcinomas,[25, 26] and are implicated in oncogenesis. ADC development in aUC has thus far focused on ErbB1 (EGFR), ErbB2 (HER2), and ErbB3 (HER3).

The HER2-targeting ADC trastuzumab deruxtecan (T-DXd) is already an established therapy in breast cancer and is being investigated in aUC.[27] T-DXd has recently garnered FDA approval for all tumour types with high HER2 expression by immunohistochemistry (IHC 3+). T-DXd combines trastuzumab (HER2-targeting monoclonal antibody) to deruxtecan, a topoisomerase I inhibitor more potent than SN-38 (the active metabolite of irinotecan) with a DAR of 8:1.[28] DESTINY-PanTumour2 was a phase II basket trial that assessed T-DXd in patients with a variety of HER2-expressing tumours after prior lines of therapy. In the UC cohort (n=41), an ORR of 39% was observed, with a median progression-free survival (mPFS) of 7.0 months, and mOS of 12.8 months **(Table 1)**. Notably, the IHC 3+ subgroup (n=16) had a higher ORR of 56.3%, mPFS of 7.4 months, and mOS of 13.4 months. With respect to toxicity, T-DXd carries the unique risk of pneumonitis/interstitial lung disease, observed in 10.5% of the study population. T-DXd holds promise for aUC with high HER2 expression, and larger trials and/or real-world evidence are needed to better understand the safety and efficacy of this agent.

ADC	Target	Payload	Phase	Study and Design	Primary Outcomes	Approvals
Enfortumab vedotin	Nectin-4	MMAE	Phase III	EV 302 – 1L EV + Pembro vs chemo	mOS: 31.5 mo vs 16.1 mo (HR 0.47; 95% CI 0.38 - 0.58) mPFS: 12.5 mo vs 6.3 mo (HR 0.45; 95% CI 0.38 – 0.54)	FDA Health Canada EMA
				EV 301 – 3L EV vs chemo (post ICI and platinum-based chemo)	mOS: 12.9 mo vs 8.9 mo (HR 0.70; 95% CI 0.58 - 0.85)	
				EV 303 – Peri-operative EV + Pembro vs chemo (Cisplatin-ineligible)	Ongoing (NCT03924895)	
				EV 304 - Peri-operative EV + Pembro vs chemo(Cisplatin-ineligible)	Ongoing (NCT04700124)	
			Phase II	EV 201 – 2L EV post-ICI in platinum-ineligible	ORR = 52%	
BT8009 (BTC)	Nectin-4	MMAE	Phase II/III	Duravelo-2	Ongoing	
			Phase I/II	BT8009-100	ORR = 50%	
Trastuzumab deruxtecan	HER2	Dxd	Phase II	DESTINY-PanTumor02	ORR = 39.9% (56.3% for IH3+)	FDA (IHC3+)
Disitamab vedotin	HER2	MMAE	Phase III	DV-001 – DV + pembro vs chemo	Ongoing	
			Phase II	RC48-C005 – 2L DV in IHC 2+ or 3+ RC48-C009 – 3L DV in IHC 2+ or 3+ RC48-C011 – 2L DV in HER2 negative	ORR = 51.2% ORR = 46.9% ORR = 26.3%	
Sacituzumab govitecan	Trop-2	SN-38	Phase III	TROPiCS-04	Did not meet primary endpoint of OS	FDA
			Phase II	TROPHY-U-01 - Cohort 1 – 3L SG post ICI and chemo - Cohort 2 – 2L SG post ICI (platinum-ineligible) - Cohort 3 – 2L SG + pembrolizumab post chemo	 ORR = 28% ORR = 32% ORR = 41%	
Datopotamab deruxtecan	Trop-2	Dxd	Phase II	TROPION-PanTumor03	Ongoing	
			Phase I	TROPION-PanTumor01	ORR = 27%	
BL-B01D1	EGFR & HER3 (Bispecific)	Ed-04	Phase II	BL-B01D1-201	ORR = 41%	

Table 1. Antibody-drug conjugates in advanced and metastatic urothelial carcinoma at or near-clinical use as of Sep. 2024; *courtesy of Pooya Dibajnia, BSc (Hons), MD, FRCPC and Aly-Khan Lalani, BSc (Hons), MD, FRCPC*

Abbreviations: BTC: bicyclic toxic conjugate; **CI:** confidence interval; **Dxd:** deruxtecan; **EGFR:** epidermal growth factor; **EMA:** European Medicines Agency; **EV:** enfortumab vedotin; **FDA:** Food and Drug Administration; **HER2:** human epidermal growth factor receptor 2; **HER3:** human epidermal growth factor receptor 3; **HR:** hazard ratio; **ICI:** immune checkpoint inhibitor; **IHC:** immunohistochemistry; **MMAE:** monomethyl auristatin E; **mOS:** median overall survival; **mPFS:** medial progression free survival; **mos:** months; **ORR:** objective response rate; **Pembro:** pembrolizumab; **Trop-2:** trophoblast cell surface antigen-2; **1L:** first-line; **2L:** second-line; **3L:** third-line

Disitimab vedotin is a novel HER2-targeting monoclonal antibody conjugated to the microtubule destabilizer MMAE via a protease-cleavable linker.[29] Two phase II trials have evaluated its efficacy in pre-treated aUC patients with HER2 IHC 2+ or 3+ expression **(Table 1)**.[29, 30] Notably, these trials were conducted in Asia, where the incidence of upper tract UC approached nearly 50% of the study population. In the combined analysis (n=107), the ORR was 50.5%, mPFS 5.9 months, and mOS 14.2 months. Subgroup analysis demonstrated a higher response rate for patients with IHC 2+ with fluorescence *in situ* hybridization (FISH) positivity, or IHC 3+ (ORR = 62.2%). Commonly observed toxicities included peripheral neuropathy (68.2%), neutropenia (50.5%), and liver enzyme elevation (42.1%). Similar to EV, the high incidence of peripheral neuropathy is attributable to its payload MMAE. DV currently holds Breakthrough Therapy designation from the FDA. The global phase III trial DV-001 is set to investigate the combination of DV and pembrolizumab in previously untreated patients with high HER2 expression compared to first-line chemotherapy.[31]

Emerging ADCs that employ bispecific antibodies to target two ErbB receptors is a novel approach that aims to improve efficacy of ADCs. BL-B01D1 is a first-in-class EGFR and HER3 targeting bispecific ADC. It contains an anti-EGFR monoclonal antibody fused to two anti-HER3 single chain variable fragments, which is linked to the topoisomerase inhibitor Ed-04 using a cleavable tetrapeptide-based cathepsin linker **(Figure 1)**.[32] This has been evaluated in a phase II trial involving previously treated patients. An ORR of 75.0% was observed in the cohort of patients with one prior line of therapy (n=12), and an ORR of 40.7% in patients with two or more previous lines of therapy (n=27).[33] Notably, biomarker analysis from this study has demonstrated good clinical activity regardless of level of EGFR/HER3 IHC expression. Common side effects included anemia (82%), thrombocytopenia (62%), neutropenia (56%), anorexia (47%) and nausea (44%). This first-in-class bispecific ADC holds promise across a spectrum of EGFR/HER3 expressions and requires further evaluation within a larger population.

Trop-2

Trop-2 is a cell surface glycoprotein implicated in signalling pathways of cell proliferation, migration, and invasion. It is highly expressed in many epithelial carcinomas, including UC.[34]

Sacituzumab govitecan (SG) incorporates the topoisomerase I inhibitor SN-38 as its payload and a hydrolysable pH-dependent linker.[35] In aUC, SG initially gained FDA Accelerated Approval after the results of a phase II trial in patients pre-treated with ICI and chemotherapy demonstrated an ORR of 28% and mOS of 10.9 months.[36-38] SG also demonstrated efficacy in cisplatin-ineligible patients previously treated with ICI, with an ORR of 32% and mOS of 13.5 months **(Table 1)**.[39] However, the confirmatory phase III TROPiCS-04 trial comparing SG to single-agent chemotherapy in a pre-treated population did not meet its primary endpoint for OS **(Table 1)**.[40] At the time of writing, SG does not have Health Canada approval in UC. Further research into the use of SG in combination with other agents are ongoing (NCT03547973).[41]

Datopotomab deruxtecan (Dato-DXd) is another trop-2-targeting ADC currently under investigation. It contains the payload deruxtecan and a tetrapeptide-based cleavable linker that is plasma-stable. In a phase I basket trial that included 18 patients with heavily pre-treated aUC, the ORR was found to be 27.8%, with one patient achieving a complete response **(Table 1)**.[42] Currently, a phase II trial is underway to study Dato-DXd as a monotherapy and in combination with other agents (NCT05489211).[43]

These early phase studies have demonstrated SG and Dato-Dxd to have comparable toxicities largely attributed to their topoisomerase inhibitor payloads, including cytopenias, stomatitis, diarrhea, and febrile neutropenia.[36, 42] Similar to irinotecan, patients with *UGT1A1* polymorphisms appear to have a higher incidence of neutropenia.[44] Rare instances of pneumonitis have been reported for both ADCs.[38, 42] Further data is needed to better describe optimal dosing, the need for prophylactic medications (e.g. granulocyte colony-stimulating factor [G-CSF]), and the role of routine *UGT1A1* testing to mitigate toxicities.

Future Directions

Currently, EV is an established standard of care for the treatment of aUC in Canada; specifically, it is available in the post-chemotherapy and post-ICI setting and approval is anticipated with pembrolizumab as a first-line standard. There are opportunities to further

improve outcomes by exploring response to ADCs in different subgroups of UC, understanding resistance mechanisms, and examining the potential of combining ADCs with other therapies. Importantly, experience and education around combination use will help ensure safe delivery and utility in the academic and community settings – where much of mUC care can occur.

Histologic and molecular variations in UC warrant further study to identify differential responses to ADCs. Historically, variant histologies of UC, such as sarcomatoid and plasmacytoid differentiation, have been associated with worse outcomes. For EV, a retrospective analysis of patients with variant histologies (n=164) found an ORR of 35-56% in those with combined urothelial and variant components. This included squamous, micropapillary, plasmacytoid, sarcomatoid, adenocarcinoma, nested, and lipid cell variants. However, neuroendocrine/small cell differentiation was associated with an unfortunate 0% response rate to EV (n=9).[45] Moreover, patients with pure variant histologies (i.e., without a urothelial component) had markedly worse response rates. Prospective studies of variant histologies are currently ongoing for EV (NCT05756569), and it is likely that for certain histologies (i.e. neuroendocrine), chemotherapy may remain as the preferred upfront treatment.[46]

Understanding resistance mechanisms to ADCs is critically important in the context of the evolving horizon scan of systemic therapies. From a cellular perspective, resistance to ADCs can develop due to downregulation of the cell surface target (e.g. nectin-4),[47] or resistance to the payload.[48] Sequencing trials have demonstrated limited efficacy of serial ADCs despite different targets and payloads. In one trial involving 82 heavily pre-treated patients, sequencing SG after EV resulted in an ORR of 10%.[49] Given that SG and EV have different payloads and targets, this suggests other mechanisms of resistance are at play, and further research in this area is needed.

Several ongoing studies are examining combinations of two ADCs, as well as ADCs with other therapies. The ongoing phase I DAD trial is evaluating the combination of SG and EV in patients previously treated with platinum chemotherapy and ICIs, while the DAD-IO trial aims to evaluate the triplet combination of SG, EV, and pembrolizumab in the first-line setting (NCT04724018).[50] Other early phase trials are evaluating the combination of EV with erdafitinib (fibroblast growth factor receptor [FGFR] inhibitor),[51] cabozantinib (multi-target tyrosine kinase inhibitor),[52] and evorpacept (CD47 inhibitor).[53]

Conclusions

ADCs targeting nectin-4, trop-2, and the ErbB family are revolutionizing the treatment of aUC. EV has shown significant efficacy in the first- and subsequent-line settings and should be considered the standard of care globally. HER2-targeting ADCs T-DXd and DV show great promise in the subgroup of patients with high HER2 expression, with results from larger trials anticipated. Early evidence for trop-2 targeting ADCs is pending confirmatory phase III outcomes. Bispecific antibodies are an evolutionary step in the engineering of ADCs that may further improve efficacy of this class of therapeutics. Further research is needed to understand resistance mechanisms to ADCs and explore their potential in combination with other therapies, including other ADCs. Given the promising results and ongoing research, it is anticipated that ADCs will have a significant treatment role earlier along the UC disease trajectory in the future.

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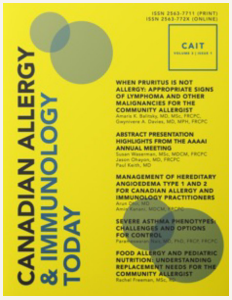

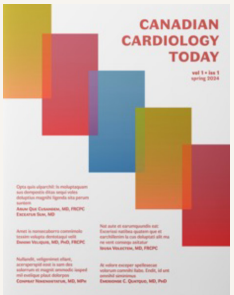

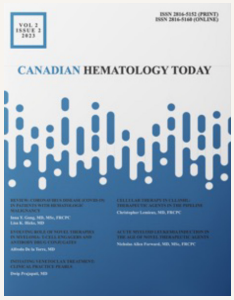

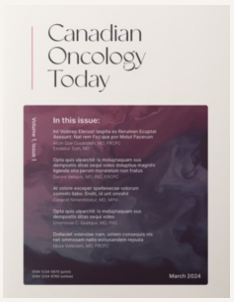

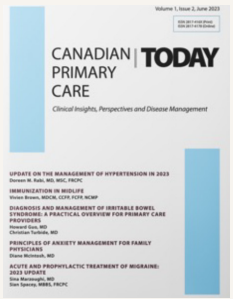

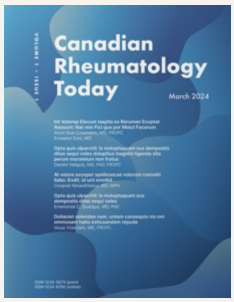

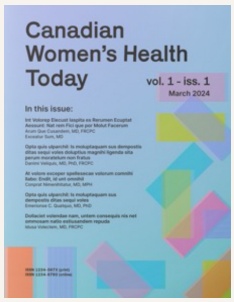

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